

Ozga
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FILE 'REGISTRY' ENTERED AT 10:53:10 ON 20 DEC 2001
E PROSTAGLANDIN E1/CN 5

L1 1 S E3
E NITROGLYCERIN/CN 5
L2 1 S E3
E "N-ACETYL CYSTEINE"/CN 5
L3 1 S E3

FILE 'CAPLUS' ENTERED AT 10:53:41 ON 20 DEC 2001

L1 1 SEA FILE=REGISTRY ABB=ON PLU=ON "PROSTAGLANDIN E1"/CN
L2 1 SEA FILE=REGISTRY ABB=ON PLU=ON NITROGLYCERIN/CN
L3 1 SEA FILE=REGISTRY ABB=ON PLU=ON N-ACETYL CYSTEINE/CN
L4 92 SEA FILE=CAPLUS ABB=ON PLU=ON (L1 OR PROSTAGLANDIN(W) ("E1" OR "EI") OR PGE1 OR PGEI OR PGE(W) (1 OR I)) AND (L2 OR NTG OR NITROGLYCERIN? OR NITRO GLYCERIN?)
L5 3 SEA FILE=CAPLUS ABB=ON PLU=ON L4 AND (L3 OR ACETYL CYSTEIN? OR NAC)

L5 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:259972 CAPLUS

DOCUMENT NUMBER: 132:293042

TITLE: Encapsulation of sensitive liquid components into a matrix to obtain discrete shelf-stable particles

INVENTOR(S): Van Lengerich, Bernhard H.

PATENT ASSIGNEE(S): General Mills, Inc., USA

SOURCE: PCT Int. Appl., 56 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000021504	A1	20000420	WO 1999-US20905	19991006
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9963872	A1	20000501	AU 1999-63872	19991006
EP 1119345	A1	20010801	EP 1999-951433	19991006
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2000004784	A	20000925	NO 2000-4784	20000925
PRIORITY APPLN. INFO.:				
			US 1998-103700	P 19981009
			US 1998-109696	P 19981124
			US 1999-233443	A 19990120
			US 1998-79060	P 19980323
			WO 1999-US4267	W 19990323
			WO 1999-US20905	W 19991006

AB A liq. encapsulant component which contains an active, sensitive encapsulant, such as a live microorganism or an enzyme dissolved or

Searcher : Shears 308-4994

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dispersed in a liq. plasticizer is admixed with a plasticizable matrix material. The matrix material is plasticizable by the liq. plasticizer and the encapsulation of the active encapsulant is accomplished at a low temp. and under low shear conditions. The active component is encapsulated and/or embedded in the plasticizable matrix component or material in a continuous process to produce discrete, solid particles. The liq. content of the liq. encapsulant component provides substantially all or completely all of the liq. plasticizer needed to plasticize the matrix component to obtain a formable, extrudable, cuttable, mixt. or dough. Removal of liq. plasticizer prior to extrusion is not needed to adjust the viscosity of the mixt. for formability. Release of an active component from the matrix may be delayed or controlled over time so that the active component is delivered when and where it is needed to perform its intended function. Controlled release, discrete, solid particles which contain an encapsulated and/or embedded component such as a heat sensitive or readily oxidizable pharmaceutically, biol., or nutritionally active component are continuously produced without substantial destruction of the matrix material or encapsulant.

IT 55-63-0, Nitroglycerin 616-91-1,

Acetylcysteine 745-65-3, Alprostadil

RL: FFD (Food or feed use); BIOL (Biological study); USES (Uses)

(encapsulation of sensitive liq. components into matrix to obtain discrete shelf-stable particles)

REFERENCE COUNT: 1

REFERENCE(S): (1) Katzen; US 3786123 A 1974 CAPLUS

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:293427 CAPLUS

DOCUMENT NUMBER: 129:8597

TITLE: Embedding and encapsulation of controlled release particles

INVENTOR(S): Van Lengerich, Bernhard H.

PATENT ASSIGNEE(S): Van Lengerich, Bernhard H., USA

SOURCE: PCT Int. Appl., 63 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9818610	A1	19980507	WO 1997-US18984	19971027
W: AU, CA, JP, NO, PL, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9749915	A1	19980522	AU 1997-49915	19971027
EP 935523	A1	19990818	EP 1997-912825	19971027
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NO 9902036	A	19990428	NO 1999-2036	19990428
PRIORITY APPLN. INFO.:			US 1996-29038	19961028
			US 1997-52717	19970716
			WO 1997-US18984	19971027

AB Controlled release, discrete, solid particles which contain an encapsulated and/or embedded component such as a heat sensitive or

readily oxidizable pharmaceutically, biol., or nutritionally active component are continuously produced without substantial destruction of the matrix material or encapsulant. A release-rate controlling component is incorporated into the matrix to control the rate of release of the encapsulant from the particles. The addnl. component may be a hydrophobic component or a high water binding capacity component for extending the release time. The plasticizable matrix material, such as starch, is admixed with at least one plasticizer, such as water, and at least one release-rate controlling component under low shear mixing conditions to plasticize the plasticizable material without substantially destroying the at least one plasticizable material and to obtain a substantially homogeneous plasticized mass. The plasticizer content is substantially reduced and the temp. of the plasticized mass is substantially reduced prior to admixing the plasticized mass with the encapsulant to avoid substantial destruction of the encapsulant and to obtain a formable, extrudable mixt. The mixt. is extruded through a die without substantial or essentially no expansion and cut into discrete, relatively dense particles. Release properties may also be controlled by precoating the encapsulant and/or coating the extruded particles with a film-forming component. An example of encapsulation of **acetylcysteine** is given using starch, polyethylene, glycerol monostearate, and vegetable oil.

IT 55-63-0, Nitroglycerin 616-91-1,

Acetylcysteine 745-65-3, Alprostadil

RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(embedding and encapsulation of controlled release particles)

L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:36460 CAPLUS

DOCUMENT NUMBER: 126:57020

TITLE: Effects of Euro-Collins, University of Wisconsin, and new extracellular-type trehalose-containing Kyoto solutions in an ex vivo rat lung preservation model

AUTHOR(S): Fukuse, Tatsuo; Hirata, Toshiki; Ueda, Mitsuhiro; Hitomi, Shigeki; Wada, Hiromi

CORPORATE SOURCE: Department of Thoracic Surgery, Chest Disease Research Institute, Kyoto University, Kyoto, 606, Japan

SOURCE: Transplantation (1996), 62(9), 1212-1217
CODEN: TRPLAU; ISSN: 0041-1337

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors have previously reported the effects of trehalose-based extracellular-type Kyoto (ET-K) soln. in lung preservation. Now, they have developed a new ET-K soln. by adding 3 substances: N-acetyl cysteine, dibutyl CAMP, and **nitroglycerin**, to the ET-K soln. The effects of this new ET-K soln. in lung preservation were studied and compared with Euro-Collins (EC) and University of Wisconsin (UW) solns. using an ex vivo rat reperfusion model. The perfusion circuit was initiated by 30 mL of fresh mixed venous blood obtained from 3 heparinized rats. By means of a double-head roller pump, the blood passed from the venous blood reservoir through the pulmonary artery to be

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perfused in the examd. lung. The lung effluent was returned at the same flow rate to the deoxygenator fresh lung. Four exptl. groups were allocated. In group 1 (fresh group), the lung was flushed with saline and reperfused immediately. In the other groups (group 2: new ET-K group; group 3: UW group; and group 4: EC group), the lung was flushed with the new ET-K and PGE1, UW and PGE1, and EC and PGE1, resp. After 17-h preservation, the preserved lung was reperfused. In all animals of the EC group, ventilation of the exptl. lung was discontinued at 20 min after reperfusion because of the exudate in the endotracheal tube that resulted from pulmonary edema. The shunt fraction, pulmonary arterial pressure, and peak inspiratory pressure in the new ET-K and UW groups were significantly better than those in the EC group, but were almost equal to those in the fresh group. The postpreservation pulmonary functions with the new ET-K soln. were better than those with the EC soln. and were equal to those with the UW soln. This new soln. is expected to contribute to the increase in donor lungs for clin. lung transplantation. In addn., this ex vivo rat reperfusion model is simple and highly reliable and can be widely used in the studies of pulmonary preservation.

(~~FILED~~ MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 10:56:47 ON 20 DEC 2001)

9 S L5

6 DUP REM L6 (3 DUPLICATES REMOVED)

L7 ANSWER 1 OF 6 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001161946 EMBASE
TITLE: [Expertenforum der DGAI: Hemodynamic active drugs in critical care medicine - Glossar, calculation of hemodynamics and oxygen transport].
GLOSSAR UND BERECHNUNGEN VON HAMODYNAMIK UND SAUERSTOFFTRANSPORT.
AUTHOR: Burchardi H.
CORPORATE SOURCE: Dr. H. Burchardi, Zentrum Anasthesiologie, Rettungs- und Intensivmedizin, Univ.-Klinikum Gottingen, Robert-Koch-Str. 40, 37075 Gottingen, Germany
SOURCE: Intensivmedizin und Notfallmedizin, (2001) 38/3 (216-220).
ISSN: 0175-3851 CODEN: INNOEK
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: German

L7 ANSWER 2 OF 6 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 97086569 MEDLINE
DOCUMENT NUMBER: 97086569 PubMed ID: 8932258
TITLE: Effects of Euro-Collins, University of Wisconsin, and new extracellular-type trehalase-containing Kyoto solutions in an ex vivo rat lung preservation model.
AUTHOR: Fukuse T; Hirata T; Ueda M; Hitomi S; Wada H
CORPORATE SOURCE: Department of Thoracic Surgery, Chest Disease Research Institute, Kyoto University, Sakyo-Ku, Japan.
SOURCE: TRANSPLANTATION, (1996 Nov 15) 62 (9) 1212-7.

Searcher : Shears 308-4994

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JOURNAL code: WEJ; 0132144. ISSN: 0041-1337.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970102

AB BACKGROUND: We have previously reported the effects of trehalose-based extracellular-type Kyoto (ET-K) solution in lung preservation. Now, we have developed a new ET-K solution by adding three substances--N-acetyl cysteine, dibutyl cyclic AMP, and nitroglycerin, to ET-K solution. We studied the effects of new ET-K solution in lung preservation, and compare it with Euro-Collins (EC) and University of Wisconsin (UW) solutions using an ex vivo rat reperfusion model. METHODS: The perfusion circuit was initiated by 30 ml of fresh mixed venous blood obtained from three heparinized rats. By means of a double-head roller pump, the blood passed from the venous blood reservoir through the pulmonary artery to be perfused in the examined lung. The lung effluent was returned at the same flow rate to the deoxygenator fresh lung. Four experimental groups were allocated. In group 1 (fresh group, n=6), lung was flushed with saline and reperfused immediately. In the other groups (group 2: new ET-K group, n=6; group 3: UW group, n=6; and group 4: EC group, n=6), lung was flushed with the new ET-K and prostaglandin E1 (PGE1), UW and PGE1, and EC and PGE1, respectively. After 17-hr preservation, the preserved lung was reperfused. RESULTS: In all six animals of the EC group, ventilation of the experimental lung was discontinued at 20 min after reperfusion because of the exudate in the endotracheal tube that resulted from pulmonary edema. The shunt fraction, pulmonary arterial pressure, and peak inspiratory pressure in the new ET-K and UW groups were significantly better than those in the EC group, but were almost equal to those in the fresh group. CONCLUSION: The postpreservation pulmonary functions with the new ET-K solution were better than those with the EC solution, and were equal to those with the UW solution. This new solution is expected to contribute to the increase in donor lungs for clinical lung transplantation. In addition, this ex vivo rat reperfusion model is simple and highly reliable, and can be widely used in the studies of pulmonary preservation.

L7 ANSWER 3 OF 6 MEDLINE
ACCESSION NUMBER: 96182192 MEDLINE
DOCUMENT NUMBER: 96182192 PubMed ID: 8607664
TITLE: Effective 30-hour preservation of canine lungs with modified ET-Kyoto solution.
AUTHOR: Wada H; Liu C J; Hirata T; Bando T; Kosaka S
CORPORATE SOURCE: Department of Thoracic Surgery, Chest Disease Research Institute, Kyoto University, Japan.
SOURCE: ANNALS OF THORACIC SURGERY, (1996 Apr) 61 (4) 1099-105.
Journal code: 683; 15030100R. ISSN: 0003-4975.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

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FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 19960531
Last Updated on STN: 19980206
Entered Medline: 19960517

AB BACKGROUND: With the aim of developing a preservation solution that can preserve donor lungs reliably for a long time, we prepared a modified ET-Kyoto solution by adding **N-acetylcysteine**, **nitroglycerin**, and dibutyladenosine 3', 5'-cyclic phosphate to the previously reported ET-Kyoto solution, which contains trehalose, gluconate, and hydroxyethyl starch. In this study, we examined the efficacy of modified ET-Kyoto solution in 30-hour lung preservation. METHODS: Twenty five pairs of adult mongrel dogs were divided into four groups. Donor lungs were flushed with modified ET-Kyoto solution (n = 9), with ET-Kyoto solution (n = 6), with University of Wisconsin solution group (n = 6), or with ET-Kyoto solution plus the solvents of **nitroglycerin** (ethanol and propylene glycol) (n = 4), then stored at 4 degrees C for 30 hours. All animals were treated with **prostaglandin E1**. Left lungs were transplanted and reperfused for 6 hours. RESULTS: With respect to arterial oxygen tension, peak inspiratory pressure, and wet-to-dry lung weight ratio, modified ET-Kyoto solution was significantly superior to ET-Kyoto solution. The modified ET-Kyoto solution was significantly superior to University of Wisconsin solution with respect to survival rate, arterial oxygen tension, and wet-to-dry lung weight ratio. Ultrastructural findings supported these results. CONCLUSIONS: These results suggest that modified ET-Kyoto solution is superior to University of Wisconsin solution for 30-hour lung preservation.

L7 ANSWER 4 OF 6 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96296962 EMBASE
DOCUMENT NUMBER: 1996296962
TITLE: Supportive pharmacotherapy for patients with acute respiratory distress syndrome.
AUTHOR: Krafft P.; Fridrich P.; Hammerele A.F.; Steltzer H.
CORPORATE SOURCE: Dept. of Anesth./Gen. Intens. Care, University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria
SOURCE: Acta Anaesthesiologica Scandinavica, Supplement, (1996) 40/109 (65-69).
ISSN: 0515-2720 CODEN: AASXAP
COUNTRY: Denmark
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
024 Anesthesiology
037 Drug Literature Index
LANGUAGE: English

L7 ANSWER 5 OF 6 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94290499 EMBASE
DOCUMENT NUMBER: 1994290499
TITLE: Diagnosis and management of acute lung injury.
AUTHOR: Marinelli W.A.; Ingbar D.H.
CORPORATE SOURCE: Div. of Pulmonary/Critical Care Med., Hennepin County Medical Center, 701 Park Avenue, Minneapolis, MN 55415, United States

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SOURCE: Clinics in Chest Medicine, (1994) 15/3 (517-466).
ISSN: 0272-5231 CODEN: CCHMDA
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
015 Chest Diseases, Thoracic Surgery and
Tuberculosis
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Severe acute lung injury, also known as the adult respiratory distress syndrome (ARDS), is a dynamic and explosive clinical syndrome which exacts a mortality of approximately 50%. The criteria for the diagnosis of severe acute lung injury include five principal elements: hypoxemia despite high concentrations of supplemental oxygen, diffuse pulmonary infiltrates on chest radiographs, decreased lung compliance, appropriate antecedent history, and the absence of congestive heart failure. Identifying an appropriate antecedent history requires consideration of a diverse group of etiologies which may injure alveolar structures via either the air-lung or blood-lung interface. The management of patients with acute lung injury should be approached with four principal goals: (1) cardiopulmonary resuscitation and stabilization; (2) rapid identification and elimination of the cause of lung injury; (3) achieving adequate tissue oxygen delivery and support of other end-organs; and (4) prevention, recognition, and aggressive treatment of any complications that develop during the course of therapy. Recent observations have suggested that conventional methods of positive-pressure ventilation may indirectly injure alveolar tissue, thereby perpetuating lung injury. Furthermore, the optimal use of fluid and hemodynamic support remains controversial. Thus, controlled clinical trials are necessary to develop oxygenation, ventilatory, and hemodynamic support strategies which optimize recovery and minimize further injury and to define the role of newer pharmacologic agents in the prevention and treatment of acute lung injury.

L7 ANSWER 6 OF 6 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 85065770 EMBASE
DOCUMENT NUMBER: 1985065770
TITLE: Anticholinergics, cromolyn, and other occasionally useful drugs.
AUTHOR: George R.B.; Payne D.K.
CORPORATE SOURCE: Pulmonary Diseases Section, Louisiana State University Medical School, Shreveport, LA 71130, United States
SOURCE: Clinics in Chest Medicine, (1984) 5/4 (685-693).
CODEN: CCHMDA
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
007 Pediatrics and Pediatric Surgery
006 Internal Medicine
LANGUAGE: English
AB This article will discuss the anticholinergic agents and cromolyn,

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as well as a group of less commonly used anti-asthma-drugs. Some of the agents are used to produce bronchodilation during the acute asthma attack, while others are used to prevent bronchospasm. Some are nonspecific agents designed to improve mucus clearance or treat associated problems such as upper respiratory tract symptoms and anxiety. Some have no proven benefit and some are potentially harmful.

~~FILE 'REGISTRY'~~ ENTERED AT 11:03:40 ON 20 DEC 2001
E GLUTATHIONE/CN 5

L8 1 S E3

~~FILE 'CAPLUS'~~ ENTERED AT 11:04:03 ON 20 DEC 2001

L1 1 SEA FILE=REGISTRY ABB=ON PLU=ON "PROSTAGLANDIN E1"/CN
L2 1 SEA FILE=REGISTRY ABB=ON PLU=ON NITROGLYCERIN/CN
L3 1 SEA FILE=REGISTRY ABB=ON PLU=ON N-ACETYLCYSTEINE/CN
L8 1 SEA FILE=REGISTRY ABB=ON PLU=ON GLUTATHIONE/CN
L9 499 SEA FILE=CAPLUS ABB=ON PLU=ON (L1 OR PROSTAGLANDIN OR
PGE1 OR PGEI OR PGE(W) (1 OR I)) AND (L2 OR NTG OR
NITROGLYCERIN? OR NITRO GLYCERIN? OR (NITRIC OXIDE OR
NO) (W) DONOR)
L10 19 SEA FILE=CAPLUS ABB=ON PLU=ON L9 AND (L3 OR L8 OR
GLUTATHIONE OR ACETYLCYSTEIN? OR (ACETYL OR AC) (W) CYSTEIN
? OR NAC)

L11 16 L10 NOT L5

L11 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:868945 CAPLUS
TITLE: Infrared thermography and methods of use
INVENTOR(S): Marek, Przemyslaw A.; Trocha, Andrzej M.
PATENT ASSIGNEE(S): Marek, Przemyslaw, USA
SOURCE: U.S. Pat. Appl. Publ., 31 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001046471	A1	20011129	US 2001-850081	20010508
PRIORITY APPLN. INFO.:			US 2000-202935	P 20000509

AB The present invention describes rapid noninvasive methods for measuring vasodilation or changes in blood flow in a patient following administration of at least one compd. that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or at least one vasoactive agent. The method comprises the administration of at least one compd. that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or at least one vasoactive agent to the patient followed by monitoring the temp. change of an area of interest using IR thermog. The present invention provides methods for diagnosing diseases or disorders related to vasodilation and changes in blood flow, such

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as, sexual dysfunction, Raynaud's syndrome, inflammation, hypertension, gastrointestinal disorders and central nervous system disorders. The sexual dysfunction is preferably female sexual dysfunction and female sexual arousal. The vasoactive agents include potassium channel activators, calcium channel blockers, .alpha.-adrenergic receptor antagonists, .beta.-blockers, phosphodiesterase inhibitors, adenosine, ergot alkaloids, vasoactive intestinal peptides, **prostaglandins**, dopamine agonists, opioid antagonists, endothelin antagonists and thromboxane inhibitors. The present invention can also be used to screen and identify drug candidates for treating diseases, disorders and conditions resulting from vasodilation or changes in blood flow. The present invention also describes compns. comprising at least one S-nitrosothiol compd. for diagnosing, monitoring and/or treating female sexual dysfunctions.

IT **70-18-8, Glutathione**

RL: RCT (Reactant); RACT (Reactant or reagent)

(IR thermog. for measuring vasodilation or changes in blood flow following administration of **nitric oxide donor**)

L11 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:338762 CAPLUS

DOCUMENT NUMBER: 134:362292

TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile

INVENTOR(S): Farr, Spencer

PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA

SOURCE: PCT Int. Appl., 222 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 1999-165398 P 19991105
US 2000-196571 P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to det. the hypersensitivity of individuals to a given agent, such as drug or other chem., in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes assocd. with

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hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes assocd. with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes assocd. with hypersensitivity. The expression of the genes predetd. to be assocd. with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and app. useful for identifying hypersensitivity in a subject are also disclosed.

IT 55-63-0, Nitroglycerin 745-65-3,
Alprostadil

RL: BAC (Biological activity or effector, except adverse); BIOL
(Biological study)

(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

L11 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:666601 CAPLUS

DOCUMENT NUMBER: 133:256811

TITLE: Pharmaceutical compositions containing dopamine agonists in combination with **nitric oxide donors** for treating and/or preventing sexual dysfunctions

INVENTOR(S): Garvey, David S.

PATENT ASSIGNEE(S): Nitromed, Inc., USA

SOURCE: PCT Int. Appl., 48 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000054773	A1	20000921	WO 2000-US3709	20000310
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 1999-123920 P 19990312

OTHER SOURCE(S): MARPAT 133:256811

AB The present invention is directed to novel compns. comprising at least one dopamine agonist in combination with at least one **nitric oxide donor** (i.e. compds. that donate, transfer or release nitric oxide, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or are substrates for nitric oxide synthase). The novel compns. may optionally comprise at least one

therapeutic agent, such as, a vasoactive agent, an antiemetic agent, and mixts. thereof. The dopamine agonist is preferably apomorphine. The present invention is also directed to methods for treating and/or preventing sexual dysfunctions and/or enhancing sexual responses in patients. In other embodiments, the present invention is directed to methods treating or preventing neurodegenerative diseases, mitochondrial diseases, spinal cord injury, central or psychostimulant addiction, senile dementia, circulatory disorders, cardiovascular disorders, hyperprolactinemia or myopia. The compds. and/or compns. of the present invention can also be provided in the form of a pharmaceutical kit (no data).

REFERENCE COUNT:

4

REFERENCE(S):

- (1) Cooke; US 5891459 A 1999 CAPLUS
- (2) El-Rashid, Y; US 5770606 A 1998 CAPLUS
- (3) Schoenleber; US 4963568 A 1990 CAPLUS
- (4) The United States Of America; WO 9632118 A 1996 CAPLUS

L11 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:602938 CAPLUS

DOCUMENT NUMBER: 131:284381

TITLE: Platelet activation and modulation of the induction of nitric oxide synthase in the conscious rat

AUTHOR(S): Picunio, Stefania; Simioni, Monica; Doni, Maria Gabriella

CORPORATE SOURCE: Institute of Human Physiology, Faculty of Medicine and Surgery, University of Padova Via Marzolo 3, Padua, 35131, Italy

SOURCE: Life Sci. (1999), 65(14), 1463-1475

CODEN: LIFSAK; ISSN: 0024-3205

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Injection of lipopolysaccharide (LPS) (Salmonella W. Typhosa i.v. bolus) into conscious rats, induced a rapid drop of circulating platelets analogous to that induced by ADP. The animals showed a small fall in mean arterial blood pressure (MABP), an increase in heart rate and a significant increase in plasma nitrite and nitrate level. This result is consistent with the stimulation of an inducible NO synthase (i-NOS). The administration of the stable prostacyclin analog, iloprost plus ADP or LPS, significantly protected against the decrease in free platelet no. induced by ADP or LPS. The plasma nitrite and nitrate level stimulated by LPS was significantly reduced by iloprost and also by prostacyclin. These results are consistent with an inhibition of i-NOS by agents that increase the intracellular level of cAMP. The administration of the **NO donor** S-Nitroso-N-acetyl-D,L-penicillamine (SNAP) plus ADP or LPS, significantly prevented thrombocytopenia induced by ADP and by LPS. SNAP did not decrease the plasma nitrite and nitrate level stimulated by LPS; furthermore it induced a significant increase of heart rate, without affecting MABP, suggesting a direct accelerating effect of NO on the sino-atrial node. The administration of S-nitroso-glutathione (GSNO), a stable nitrosothiol, plus ADP or LPS, significantly prevented thrombocytopenia induced by ADP but not by LPS. GSNO significantly reduced the plasma nitrite and nitrate level stimulated by LPS. These data demonstrate that the L-Arginine:NO pathway in vivo may be

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modulated by prostanoids and that compds. which increase cAMP, such as iloprost, are able to protect against LPS-induced early thrombocytopenia.

REFERENCE COUNT: 41
REFERENCE(S): (1) Boughton-Smith, N; Eur J Pharmacol 1990, V191, P485 CAPLUS
(2) Bredt, D; Nature 1991, V351, P714 CAPLUS
(5) Crutchley, D; J Pharmacol Exp Ther 1994, V271, P446 CAPLUS
(6) Csako, G; Thromb Haemost 1988, V59, P378 CAPLUS
(7) Des Prez, R; J Exp Med 1961, V114, P857 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:354421 CAPLUS

DOCUMENT NUMBER: 131:14000

TITLE: Method and pharmaceutical composition for inhibiting premature rupture of fetal membranes, ripening of uterine cervix and preterm labor

INVENTOR(S): Leibovitz, Shamir

PATENT ASSIGNEE(S): Israel

SOURCE: PCT Int. Appl., 60 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9926655	A1	19990603	WO 1998-IL572	19981124
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
AU 9913492	A1	19990615	AU 1999-13492	19981124
AU 735197	B2	20010705		
EP 1034002	A1	20000913	EP 1998-957105	19981124
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, FI			
JP 2001523730	T2	20011127	JP 2000-521856	19981124
PRIORITY APPLN. INFO.:			IL 1997-122278	A 19971124
			WO 1998-IL572	W 19981124

AB A method and a pharmaceutical compn. are provided for inhibiting premature rapture of the fetal membranes, ripening of the uterine cervix and preterm labor of female mammals, including humans. The method includes the step of administering compds. for reversing at least two biochem. conditions being assocd. with the above processes. The pharmaceutical compn. includes compds. for reversing at least two biochem. conditions being assocd. with the above processes.

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IT 55-63-0, Glycerol trinitrate 616-91-1, N-Acetylcysteine

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (method and pharmaceutical compn. for inhibiting premature rupture of fetal membranes, ripening of uterine cervix, and preterm labor)

REFERENCE COUNT: 2

REFERENCE(S): (1) Milwidsky, A; Am J Obstet Gynecol 1992, V166(2), P606 CAPLUS
(2) Zeeman, G; Obstet Gynecol 1997, V89(5, Pt2), P873 CAPLUS

L11 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:766507 CAPLUS

DOCUMENT NUMBER: 130:29221

TITLE: Preparation of solid porous matrixes for pharmaceutical uses

INVENTOR(S): Unger, Evan C.

PATENT ASSIGNEE(S): Imarx Pharmaceutical Corp., USA

SOURCE: PCT Int. Appl., 139 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9851282	A1	19981119	WO 1998-US9570	19980512
W: AU, BR, CA, CN, JP, KR, NZ				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9873787	A1	19981208	AU 1998-73787	19980512
EP 983060	A1	20000308	EP 1998-921109	19980512
R: DE, FR, GB, IT, NL				
US 2001018072	A1	20010830	US 2001-828762	20010409
PRIORITY APPLN. INFO.: US 1997-46379 P 19970513				
US 1998-75477 A 19980511				
WO 1998-US9570 W 19980512				

AB A solid porous matrix formed from a surfactant, a solvent, and a bioactive agent is described. Thus, amphotericin nanoparticles were prepd. by using ZrO₂ beads and a surfactant. The mixt. was milled for 24 h.

IT 55-63-0, Nitroglycerin 70-18-8, Glutathione, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (prepn. of solid porous matrixes for pharmaceutical uses)

REFERENCE COUNT: 1

REFERENCE(S): (1) Wong; US 5569448 A 1996 CAPLUS

L11 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:753681 CAPLUS

DOCUMENT NUMBER: 130:163009

TITLE: The nitric oxide

donor sodium nitroprusside is protective in ischemia/reperfusion injury of the pancreas
Benz, Stefan; Schnabel, Rolf; Weber, Heike;

AUTHOR(S):

09/976805

Pfeffer, Frank; Wiesner, Reiko; Von Breitenbuch, Phillip; Nizze, Horst; Schareck, Wolfgang; Hopt, Ulrich T.

CORPORATE SOURCE: Department of Surgery, University of Rostock, Rostock, 18057, Germany

SOURCE: Transplantation (1998), 66(8), 994-999
CODEN: TRPLAU; ISSN: 0041-1337

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The role of nitric oxide in the ischemia/reperfusion injury of the pancreas is still unclear. In other organs, protective as well as aggravating effects have been described. We have, therefore, investigated the effect of the **nitric oxide donor** sodium nitroprusside on pancreatic ischemia/reperfusion injury. In Landrace pigs, after trans-section of the pancreas, complete vascular isolation of the pancreatic tail was performed. The tail was subjected to 3 h of warm ischemia and thereafter reperfusion (6 h). The animals were divided into a control group (n=7) and a treatment group (n=7) that received 15 mg of sodium nitroprusside after reperfusion intra-arterially into the splenic artery. The morphol. tissue damage and lipase activity in the venous effluent of the pancreas were significantly lower in the treatment group. Partial oxygen tension in the tissue after reperfusion was markedly reduced in the control group, indicating an impairment of microcirculation. In the treatment group, however, partial oxygen tension in the tissue was significantly higher (43 vs. 20 mmHg; $P < 0.014$). Furthermore, total blood flow through the pancreatic tail in the treatment group was found to be significantly higher in the late reperfusion period (14 vs. 9.5 mL/min at 5 h after reperfusion; $P < 0.05$). There is a marked impairment of pancreatic microcirculation after reperfusion. Sodium nitroprusside counteracts this impairment and has a protective effect on ischemia/reperfusion injury of the pancreas.

REFERENCE COUNT: 41

REFERENCE(S): (1) Amrani, M; Cardiovasc Res 1995, V30, P200
CAPLUS
(2) Beckman, J; Biochem Soc Trans 1993, V21, P330 CAPLUS
(5) Beresewicz, A; Cardiovasc Res 1995, V30, P1001 CAPLUS
(7) Brehe, J; Anal Biochem 1976, V74, P189 CAPLUS
(10) Caldwell, M; Eur J Pharmacol 1995, V285, P203 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:390582 CAPLUS

DOCUMENT NUMBER: 129:157276

TITLE: Role of nitric oxide and **prostaglandins** in mechanically induced bone formation

AUTHOR(S): Chow, J. W. M.; Fox, S. W.; Lean, J. M.; Chambers, T. J.

CORPORATE SOURCE: Department of Histopathology, St. George's Hospital Medical School, London, UK

SOURCE: J. Bone Miner. Res. (1998), 13(6), 1039-1044
CODEN: JBMREJ; ISSN: 0884-0431

09/976805

PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have previously shown that **prostaglandins** (PG) and nitric oxide (NO) are required in the induction of bone formation by mech. stimulation. The authors therefore tested the ability of **NO donors**, S-nitroso-N-acetyl-D,L-penicillamine (SNAP), and S-nitroso-**glutathione** (GSNO) to mimic or augment the osteogenic response of bone to a minimal mech. stimulus. In rats administered vehicle or the vasodilator hydralazine, stimulation of the 8th caudal vertebra increased bone formation. In animals treated with SNAP or GSNO, there was significant potentiation of this osteogenic response. The bone formation rate in nonloaded vertebrae was unaffected by administration of the **NO donors**. The authors also found that while inhibition of either PG or NO prodn. at the time of loading caused a partial suppression of c-fos mRNA expression in the loaded vertebrae, administration of indomethacin and NG-monomethyl-L-arginine together markedly suppressed c-fos expression. This suggests that although both PG and NO are required in mech. induced osteogenesis, they appear to be generated largely independently of each other. Moreover, while exogenous NO potentiates the stimulatory effect of mech. loading on bone formation, the lack of effect in nonloaded vertebrae suggests that NO is necessary but not sufficient for induction of bone formation.

L11 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:82514 CAPLUS

DOCUMENT NUMBER: 128:212969

TITLE: Characterization of NS 2028 as a specific inhibitor of soluble guanylyl cyclase

AUTHOR(S): Olesen, Soren-Peter; Drejer, Jorgen; Axelsson, Oskar; Moldt, Peter; Bang, Lone; Nielsen-Kudsk, Jens Erik; Busse, Rudi; Millsch, Alexander

CORPORATE SOURCE: NeuroSearch, Glostrup, DK-2600, Den.

SOURCE: Br. J. Pharmacol. (1998), 123(2), 299-309

CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Stockton Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The heme-contg. sol. guanylyl cyclase (.alpha.1/.beta.1-heterodimer) is a major intracellular receptor and effector for nitric oxide (NO) and carbon monoxide (CO) and mediates many of their biol. actions by increasing cyclic GMP. We have synthesized new oxadiazolobenzoxazines and have assessed their inhibitory actions on guanylyl cyclase activity in vitro, on the formation of cyclic GMP in cultured cells and on the NO-dependent relaxation of vascular and non-vascular smooth muscle. Sol. guanylyl cyclase, purified to homogeneity from bovine lung, was inhibited by 4H-8-bromo-1,2,4-oxadiazolo(3,4-d)benz(b)(1,4)oxazin-1-one (NS 2028) in a concn.-dependent and irreversible manner (IC50 30 nM for basal and 200 nM for NO-stimulated enzyme activity). Evaluation of the inhibition kinetics according to Kitz & Wilson yielded a value of 8 nM for Ki, the equil. const. describing the initial reversible reaction between inhibitor and enzyme, and 0.2 min-1 for the rate const. k3 of the subsequent irreversible inhibition. Inhibition was accompanied by a shift in the solet absorption max. of the enzyme's heme cofactor from 430 to 390 nm. S-nitroso-**glutathione**

-enhanced sol. guanylyl cyclase activity in homogenates of mouse cerebellum was inhibited by NS 2028 (IC₅₀ 17 nM) and by 17 structural analogs in a similar manner, albeit with different potency, depending on the type of substitution at positions 1, 7 and 8 of the benzoxazin structure. Small electroneg. ligands such as Br and Cl at position 7 or 8 increased and substitution of the oxygen at position 1 by -S-, -NH- or -CH₂-decreased the inhibition. In tissue slices prepd. from mouse cerebellum, neuronal NO synthase-dependent activation of sol. guanylyl cyclase by the glutamate receptor agonist N-methyl-D-aspartate was inhibited by NS 2028 (IC₅₀ 20 nM) and by two of its analogs. Similarly, 3-morpholino-sydnonimine (SIN-1)-elicited formation of cyclic GMP in human cultured umbilical vein endothelial cells was inhibited by NS 2028 (IC₅₀ 30 nM). In **prostaglandin** F₂.alpha.-constricted, endothelium-intact porcine coronary arteries NS 2028 elicited a concn.-dependent increase (65%) in contractile tone (EC₅₀ 170 nM), which was abolished by removal of the endothelium. NS 2028 (1 .mu.M) suppressed the relaxant response to **nitroglycerin** from 88.3 +/- 2.1 to 26.8 +/- 6.4% and induced a 9 fold rightward shift (EC₅₀ 15 Mm) of the concn.-relaxation response curve to **nitroglycerin**. It abolished the relaxation to sodium nitroprusside (1 .mu.M), but did not affect the vasorelaxation to the KATP channel opener cromakalim. Approx. 50% of the relaxant response to sodium nitroprusside was recovered after 2 h washout of NS 2028. In phenylephrine-precontracted, endothelium-denuded aorta of the rabbit NS 2028 (1 .mu.M) did not affect relaxant responses to atrial natriuretic factor, an activator of particulate guanylyl cyclase, or forskolin, an activator of adenylyl cyclase. NO-dependent relaxant responses in non-vascular smooth muscle were also inhibited by NS 2028. The **nitroglycerin**-induced relaxation of guinea-pig trachea precontracted by histamine was fully inhibited by NS 2028 (1 .mu.M), whereas the relaxations to terbutaline, theophylline and vasoactive intestinal polypeptide (VIP) were not affected. The relaxant responses to elec. field stimulation of non-adrenergic, non-cholinergic nerves in the same tissue were attenuated by 50% in the presence of NS 2028 (1 .mu.M). 8 NS 2028 and its analogs, one of which is the previously characterized 1H-[1,2,4]oxadiazolo[4,3,-a]quinoxalin-1-one (ODQ), appear to be potent and specific inhibitors of sol. guanylyl cyclase present in various cell types. Oxidn. and/or a change in the coordination of the heme-iron of guanylyl cyclase is a likely inhibitory mechanism.

L11 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:532196 CAPLUS

DOCUMENT NUMBER: 127:200050

TITLE: Nitrosated and nitrosylated .alpha.-adrenergic receptor antagonist compounds, preparation thereof, compositions containing them, and use in treatment of human impotence or erectile dysfunction

INVENTOR(S): Garvey, David S.; Schroeder, Joseph D.; Saenz De Tejada, Inigo

PATENT ASSIGNEE(S): Nitromed, Inc., USA; Garvey, David S.; Schroeder, Joseph D.; Saenz De Tejada, Inigo

SOURCE: PCT Int. Appl., 96 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

09/976805

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9727749	A1	19970807	WO 1997-US1294	19970128
W: AU, CA, IL, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9717562	A1	19970822	AU 1997-17562	19970128
AU 721247	B2	20000629		
JP 20000505424	T2	20000509	JP 1997-537755	19970128
EP 1018879	A1	20000719	EP 1997-904887	19970128
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6294517	B1	20010925	US 1998-145143	19980901
US 6323211	B1	20011127	US 1999-285048	19990402
PRIORITY APPLN. INFO.:			US 1996-595732	A 19960202
			US 1996-714313	A 19960918
			WO 1997-US1294	W 19970128
			US 1998-145143	A2 19980901

OTHER SOURCE(S): MARPAT 127:200050

AB Disclosed are nitrosated and nitrosylated .alpha.-adrenergic receptor antagonists; compns. of an .alpha.-adrenergic receptor antagonist optionally substituted with .gtoreq.1 NO or NO2 moiety, and a compd. that donates, transfers, or releases nitric oxide as a charged species, i.e., nitrosonium or nitroxyl, or as the neutral species, nitric oxide; and uses for each of them in treating human impotence or erectile dysfunction. Prepn. of compds. of the invention, e.g. N-(N-L-.gamma.-glutamyl-S-nitroso-L-cysteinyl)glycine and 4-[2-(dimethylamino)ethoxy]-2-methyl-5-(1-methylethyl)phenol-(3-S-nitroso-3-methylbutyric acid)ester. The effect of selected compds. on erectile response in rabbits was detd.

IT 745-65-3, Prostaglandin E1

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(phentolamine and papaverine and; nitrosated and nitrosylated .alpha.-adrenergic receptor antagonist compds., prepn., compns., adrenergic antagonist-NO donor combinations, and use in treatment of human impotence or erectile dysfunction)

IT 70-18-8, Glutathione, reactions

RL: RCT (Reactant)
(reaction; nitrosated and nitrosylated .alpha.-adrenergic receptor antagonist compds., prepn., compns., adrenergic antagonist-NO donor combinations, and use in treatment of human impotence or erectile dysfunction)

L11 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1996:680535 CAPLUS

DOCUMENT NUMBER: 126:1543

TITLE: Endothelium-derived factors and hyperpolarization of the carotid artery of the guinea pig

AUTHOR(S): Corriu, Catherine; Feletou, Michel; Canet, Emmanuel; Vanhoutte, Paul M.

CORPORATE SOURCE: Departement de pneumologie, Institut de Recherches Servier, Suresnes, 92150, Fr.

Searcher : Shears 308-4994

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SOURCE: Br. J. Pharmacol. (1996), 119(5), 959-964
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Transmembrane potentials were recorded from isolated carotid arteries of the guinea pig superfused with modified Krebs-Ringer bicarbonate soln. Smooth muscle cells were impaled from the adventitial side with intracellular glass microelectrodes filled with KCl (30-80 M.OMEGA.). Acetylcholine (1 .mu.M) in the presence of inhibitors of nitric oxide synthase, (N.omega.-nitro-L-arginine (L-NOARG) 100 .mu.M) and cyclo-oxygenase, (indomethacin 5 .mu.M) induced an endothelium-dependent hyperpolarization (-18.9 mV). In the presence of these two inhibitors, S-nitroso-L-glutathione (10 .mu.M), sodium nitroprusside (10 .mu.M), 3-morpholinosydnonimine (SIN-1, 10 .mu.M) and iloprost (0.1 M) induced endothelium-independent hyperpolarizations of the smooth muscle cells (resp.: -16.0, -16.3, -12.8, and -14.5 mV). The addn. of glibenclamide (1 .mu.M) did not influence the acetylcholine-induced L-NOARG/indomethacin-resistant hyperpolarization (-18.0 mV). In contrast, the responses induced by S-nitroso-L-glutathione, sodium nitroprusside, SIN-1 and iloprost were abolished (changes in membrane potential: -0.8, 1.3, 4.5, and 0.3 mV, resp.). In the presence of NO synthase and cyclo-oxygenase inhibitors, charybdotoxin (0.1 .mu.M) or apamin (0.5 .mu.M) did not influence the hyperpolarization produced by acetylcholine. However, in the presence of the combination of charybdotoxin and apamin, the acetylcholine-induced L-NOARG/indomethacin-resistant hyperpolarization was converted to a depolarization (4.4 mV) while the endothelium-independent hyperpolarizations induced by S-nitroso-L-glutathione, sodium nitroprusside, SIN-1 and iloprost were not affected significantly (resp.: -20.4, -22.5, -14.5, and -14.5 mV). In the presence of the combination of charybdotoxin and apamin and in the absence of L-NOARG and indomethacin, acetylcholine induced a hyperpolarization (-19.5 mV). This hyperpolarization induced by acetylcholine was not affected by the addn. of indomethacin (-18.3 mV). In the presence of the combination of charybdotoxin, apamin and L-NOARG (in the absence of indomethacin), acetylcholine, in 5 out of 7 vessels, still produced hyperpolarization which was not significantly smaller (-9.1 mV) than the one obsd. in the absence of L-NOARG. These findings suggest that, in the guinea pig isolated carotid artery, the endothelium-independent hyperpolarizations induced by **NO donors** and iloprost involve the opening of KATP channels while the acetylcholine-induced endothelium-dependent hyperpolarization (resistant to the inhibition of NO-synthase and cyclo-oxygenase) involves the opening of Ca2+-activated potassium channel(s). Furthermore, in this tissue, acetylcholine induces the simultaneous release of various factors from endothelial origin: hyperpolarizing factors (NO, endothelium derived hyperpolarizing factor and **prostaglandins**) and possibly a depolarizing factor.

L11 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1995:723143 CAPLUS

DOCUMENT NUMBER: 123:102794

TITLE: Pharmaceutical compositions and use thereof for treatment of neurological diseases and

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etiotologically related symptomatology.
INVENTOR(S): Shapiro, Howard K.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 155 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9501096	A1	19950112	WO 1994-US7277	19940628
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5668117	A	19970916	US 1993-62201	19930629
AU 9472144	A1	19950124	AU 1994-72144	19940628
AU 692454	B2	19980611		
EP 707446	A1	19960424	EP 1994-921405	19940628
R: DE, FR, GB, IT				
JP 08512055	T2	19961217	JP 1994-503597	19940628
PRIORITY APPLN. INFO.:			US 1993-62201	19930629
			US 1991-660561	19910222
			US 1993-26617	19930223
			WO 1994-US7277	19940628

AB Pharmaceutical compns. for treatment of several neurol. diseases and pathophysiol.-related symptomol. in other body tissues, including peripheral neuropathies, secondary symptomol. of diabetes, Alzheimer's disease, Parkinson's disease, alc. polyneuropathy and age-onset symptomol., as well as analogous veterinary diseases, are disclosed. Spurious pathol. chem. crosslinking of normal intracellular structures is a fundamental aspect of these neurol. diseases. Covalent bond crosslinking of protein and lipid subcellular elements appear to underlie the formation of polymd. aggregates of neurofilaments and other structural proteins, and lipofuscin. Pharmacol. intervention in some neurol. diseases using water-sol., small mol. wt. primary amines or their derivs. as oral therapeutic agents, may compete with cellular protein and lipid amine groups for reaction with disease-induced carbonyl-contg. aliph. and arom. hydrocarbons. Primary pharmacol. agents include 4-aminobenzoic acid and derivs. thereof to facilitate kidney recognition and removal. This invention also includes oral use of nonabsorbable polyamine polymers and amine-related co-agents, such as chitosan, to covalently bind and sequester potentially toxic carbonyl compds. present in the diet, oral use of known antioxidant co-agents and related nutritional factors and use of the primary agent and co-agents in combination with known medicaments for treatment of these neurol. diseases.

IT 55-63-0, Trinitroglycerin 70-18-8, Glutathione, biological studies 616-91-1, N-Acetylcysteine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. for treatment of neurol. diseases contg.)

L11 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:440625 CAPLUS
DOCUMENT NUMBER: 119:40625

Searcher : Shears 308-4994

09/976805

TITLE: Organic nitrates and nitric oxide in
gastroprotection: implications for endogenous
sulfhydryls and vascular factors
AUTHOR(S): Morales, R. E.; Feelisch, M.; Szabo, S.
CORPORATE SOURCE: Dep. Pharmacol., Brigham and Women's Hosp.,
Boston, MA, USA
SOURCE: Biol. Nitric Oxide, Proc. Int. Meet., 2nd (1992)
, Meeting Date 1991, Volume 2, 270-2.
Editor(s): Moncada, Salvador. Portland Press:
London, UK.
CODEN: 59AFA7

DOCUMENT TYPE: Conference
LANGUAGE: English

AB In rats, expts. with org. nitrates revealed that
isosorbide-5-mononitrate (IS-5-MN), isosorbide dinitrate (ISDN) and
glycerol trinitrate (GTN) decreased the ethanol-induced hemorrhagic
mucosal lesions. The effect of GTN nad ISDN was dose-dependent in
reducing the hemorrhagic lesions in the stomach. Co-administration
of an ineffective dose of L-cysteine with low doses of nitrates (2
mg 100 g⁻¹) reduced hemorrhagic mucosal lesions by 82, 69 and 50%
after IS-5-MN, ISDN and GTN, resp. The SH alkylator
N-ethylmaleimide (NEM) pretreatment completely blocked the
protective effects of nitrates and the **glutathione**
synthesis inhibitor buthionine sulfoximine (BSO) decreased
protection by GTN, but only partially affected that by IS-5-MN and
ISDN (47 and 34%, resp.) as compared to the hemorrhagic mucosal
lesions seen in controls and protected animals. Administration of
the NO synthesis inhibitor NG-monomethyl-L-arginine (L-NMMA)
completely blocked the protection produced by histamine and
prostaglandin against vascular injury, as revealed by
monastral blue and hemorrhagic mucosal lesions. These results thus
indicate that administration of org. nitrates (characterized by
their vasodilating effects) reduced ethanol-induced gastric mucosal
lesions. The role of endogeneous SH becomes apparent as the
non-protective agent L-cysteine enhanced the gastroprotection by
nitrates. The abolishing by NEM and diminishing by BSO of
nitrate-induced protection further substantiate the role of thiol
groups in NO generation and mechanisms of gastroprotection. The
redn. of **prostaglandin**- and histamine-gastroprotection by
L-NMMA implicates NO as a mediator in mucosal and microvascular
protection. The authors thus conclude that an SH-sensitive prodn.
of NO from org. nitrates and the modulation of the endogenous
L-arginine: NO pathway by gastroprotective agents play an important
role in the prevention of vascular injury and hemorrhagic lesions in
the stomach.
IT 55-63-0, Glycerol trinitrate
RL: BIOL (Biological study)
(ulcers from ethanol inhibition by, nitric oxide and mercapto
group in)

L11 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1991:156890 CAPLUS

DOCUMENT NUMBER: 114:156890

TITLE: Captopril-induced reversal of

nitroglycerin tolerance: role of

sulfhydryl group vs. ACE-inhibitory activity

AUTHOR(S): Lawson, D. L.; Nichols, W. W.; Mehta, P.; Mehta,
J. L.

09/976805

CORPORATE SOURCE: Coll. Med., Univ. Florida, Gainesville, FL,
32610, USA
SOURCE: J. Cardiovasc. Pharmacol. (1991), 17(3), 411-18
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The angiotensin-converting enzyme (ACE) inhibitor captopril has been shown to reverse vascular tolerance to **nitroglycerin** (**NTG**). Whether captopril reverses **NTG** tolerance by providing sulfhydryl (SH) groups or by inhibiting ACE is not clear. To examine this issue, the authors treated rat aortic rings with buffer, captopril (SH +, ACE inhibitory activity +), enalaprilat (SH =, ACE inhibitory activity +), or **N-acetylcysteine** (**NAC**, SH +, ACE inhibitory activity -) prior to their contraction with epinephrine and subsequent relaxation with **NTG**. Previous exposure of **NTG**-treated rings resulted in marked resistance to the vasorelaxant effect of a subsequent exposure to **NTG** in buffer-treated rings. Both **NAC** and captopril, but not enalaprilat, potentiated the vasorelaxant effects of **NTG** during the first exposure of vascular rings to **NTG** and also prevented the development of tolerance to **NTG** during a second exposure. Buffer-treated rings showed an inability to accumulate cyclic guanosine monophosphate (GMP) in response to a second exposure to **NTG**. In contrast, both **NAC** and captopril-pretreated rings demonstrated a persistence of cyclic GMP accumulation during the second **NTG** exposure. The endothelium-dependent vasodilator acetylcholine (ACh) caused relaxation of the **NTG**-tolerant rings and also induced cyclic GMP accumulation in these rings. Prior exposure of vascular rings to ACh did not cause resistance to the subsequent vasorelaxant effects of ACh. **NAC**, captopril, and enalaprilat did not modulate the effects of ACh during either the first or subsequent exposures to ACh. In addn., indomethacin did not influence the "protective" effects of **NAC** or captopril against **NTG** tolerance. These data show that **NTG** tolerance does not cause cross-tolerance to ACh. The availability of the SH group, as in **NAC** and captopril, and not the ACE-inhibitory activity alone, as in enalaprilat, modifies **NTG** tolerance, and these effects of **NAC** or captopril are not modified by **prostaglandin** inhibition. Lastly, these agents do not modulate the vasorelaxant effects of ACh.

IT **616-91-1, N-Acetylcysteine**
RL: BIOL (Biological study)
(tolerance of aorta to **nitroglycerin**-induced relaxation response to)

IT **55-63-0, Nitroglycerin**
RL: BIOL (Biological study)
(tolerance to relaxation from, in aorta, captopril reversal of, sulfhydryl group vs. angiotensin-converting enzyme inhibition in)

L11 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1990:503430 CAPLUS

DOCUMENT NUMBER: 113:103430

TITLE: Method and apparatus for administering
dehydrated drug-containing liposomes by
inhalation

INVENTOR(S): Radhakrishnan, Ramachandran; Mihalko, Paul J.;

09/976805

PATENT ASSIGNEE(S): Abra, Robert M.
SOURCE: Liposome Technology, Inc., USA
U.S., 11 pp. Cont.-in-part of U.S. Ser. No.
737,221, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4895719	A	19900123	US 1987-22937	19870306
US 5340587	A	19940823	US 1989-366299	19890613
US 5192528	A	19930309	US 1989-444360	19891201
PRIORITY APPLN. INFO.:			US 1985-737221	19850522
			US 1986-860528	19860507
			US 1986-937609	19861203
			US 1986-937607	19861203
			US 1987-22937	19870306
			US 1987-22669	19870319

AB Self-contained app. or systems and methods for delivering a selected amt. of drug, efficiently and reproducibly, in liposome-encapsulated form are described. The app. includes liposome particles formed by spray drying a dil. aq. suspension of the liposomes. The particles formed have a fine particle size, retain the majority of their originally encapsulated material, and are stable in a preferred formulation, when suspended in a fluorocarbon solvent. The liposomes are preferably formed from partially or totally satd. phospholipids and dried in a stream of heated gas whose temp. does not degrade the lipids or structural integrity of the liposomes. The app. further includes a self-contained delivery device for producing an airborne suspension of the liposomes contg. a metered dose of drug, e.g. a metered-dose spray device. Alternatively, the liposomes and a metered amt. of the liposome-entrapped drug are contained in individual packets and the delivery device is e.g. a propellant spray device designed to release a stream of aerosolized propellant particles through the packet to entrain the liposomes in the stream. Views of various embodiments of liposome delivery app. are shown. Liposomes contg. encapsulated metaproterenol sulfate (MPS) were prepd. by solvent injection, dild., and spray dried. The spray-dried liposomes were suspended in Freon 115 or Freon 114, stored for several days, and sprayed onto a moist plate for rehydration. The amt. of encapsulated drug on rehydration was .apprx.50%. This delivery system has the advantages of (a) reduced side effects due to rapid systemic drug uptake; (b) improved therapeutic action over an extended period; and (c) the ability to modulate rate of drug release from the target site.

IT 55-63-0, Nitroglycerin 616-91-1, n-Acetyl cysteine
RL: BIOL (Biological study)
(controlled-release delivery of, by phospholipid liposome inhalation, app. for)

L11 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:628838 CAPLUS
DOCUMENT NUMBER: 107:228838
TITLE: Comparative vasorelaxing profiles of nicorandil,

Searcher : Shears 308-4994

09/976805

AUTHOR(S): isosorbide dinitrate and **nitroglycerin**
in isolated coronary arteries of the dog
Ohba, Yasuhiro; Shiraki, Yasuyuki; Sakai,
Kazushige
CORPORATE SOURCE: Explor. Res. Lab., Chugai Pharm. Co., Ltd.,
Shizuoka, 412, Japan
SOURCE: Jpn. J. Pharmacol. (1987), 45(3), 397-404
CODEN: JJPAAZ; ISSN: 0021-5198
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The vasorelaxing effects of nicorandil (NCR), isosorbide dinitrate (ISDN), and **nitroglycerin** (NTG) were studied in isolated canine coronary arteries. In rings of coronary arteries precontracted with **prostaglandin** F2.alpha. or KCl (30 mM), removal of the endothelium augmented the relaxing effects of NCR; it did not affect those of ISDN and NTG. In unrubbed rings precontracted with KCl, methylene blue inhibited vasorelaxing responses to the 3 drugs. The order of the inhibition was as follows: NTG>ISDN>NCR. When the unrubbed tissue was incubated with NTG (10-5 M) or ISDN (10-4 M) for 10 min, it developed acute tolerance in relaxing response to NTG or ISDN. NCR did not develop any tolerance. Treatment with N-acetylcysteine tended to potentiate relaxant effects of NTG and to reduce the degree of acute tolerance to NTG. The results suggest that cGMP plays a role in the relaxation of the coronary artery induced by the drugs, and that the mode of the vasorelaxing action of NCR may be somewhat different from that of NTG or ISDN.

IT 55-63-0, **Nitroglycerin**
RL: PRP (Properties)
(vasorelaxing effect of, in coronary artery, mechanism of)

(FILE MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH,
JICST-EPLUS, JAPIO' ENTERED AT 11:06:39 ON 20 DEC 2001)

L12 56 S L10
L13 47 S L12 NOT L6
L14 28 DUP REM L13 (19 DUPLICATES REMOVED)

L14 ANSWER 1 OF 28 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001211871 EMBASE
TITLE: Effects of nitrovasodilators on the human
fetal-placental circulation in vitro.
AUTHOR: Zhang X.Q.; Kwek K.; Read M.A.; Donoghue J.F.;
Walters W.A.W.
CORPORATE SOURCE: M.A. Read, Division of Obstetrics/Gynaecology, John
Hunter Hospital, HRMC, Locked Bag 1, Newcastle, NSW
2310, Australia. mdmar@mail.newcastle.edu.au
SOURCE: Placenta, (2001) 22/4 (337-346).
Refs: 40
ISSN: 0143-4004 CODEN: PLACDF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 010 Obstetrics and Gynecology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB This study examines the vasorelaxation of isolated human placental

chorionic plate arteries and the perfused fetal-placental vasculature, in vitro, to a variety of nitrovasodilator compounds including glyceryl trinitrate (GTN) sodium nitroprusside (SNP), S-nitroso-N-acetylpenicillamine (SNAP), S-nitroso-N-**glutathione** (SNG) and NaNO(2). The effects of these compounds were also examined under conditions of high (>450 mmHg) and low oxygen (<50 mmHg) tension. In a separate series of experiments the effects of GTN and NaNO(2) were further investigated with addition of the antioxidants cysteine (100 .mu.M), **glutathione** (100 .mu.M) or superoxide dismutase (SOD) (30 I.U./ml). The order of nitrovasodilator potency, when added directly to isolated fetal vessels was GTN=SNP>SNAP=SNG>NaNO(2). The order under low oxygen tension was similar, GTN=SNP>SNG=SNAP.gtoeq.NaNO(2). SNG (.OMICRON.fourfold) and NaNO(2) (.OMICRON.50-fold) were significantly more potent under low oxygen conditions. Cysteine, **glutathione** and SOD were without effect on GTN induced vasodilatation. However, all three agents significantly enhanced (six- to ninefold) the effects of NaNO(2) under similar conditions. When infused directly into the fetal-placental circulation during in vitro perfusion experiments the order of potency was GTN>SNP.gtoeq.SNG.gtoeq.SNAP.gtoeq.NaNO(2). When the nitrovasodilators were infused indirectly via the maternal intervillous space the order of potency was GTN.gtoeq.SNP.gtoeq.NaNO(2).gtoeq.SNAP=SNG. Our observations suggest that there are important differences in the action of different classes of nitrovasodilator compounds on the fetal-placental circulation. The changes observed with SNG and NaNO(2) may be influenced by levels of tissue oxygenation. .COPYRG. 2001 Harcourt Publishers Ltd.

L14 ANSWER 2 OF 28 MEDLINE
 ACCESSION NUMBER: 2001683002 IN-PROCESS
 DOCUMENT NUMBER: 21586139 PubMed ID: 11728169
 TITLE: Effects of **nitric oxide**
donor and inhibitor on **prostaglandin**
E(2)-like activity, malondialdehyde and reduced
glutathione levels after skeletal muscle
 ischemia-reperfusion.
 AUTHOR: Sayan H; Babul A; Ugurlu B
 CORPORATE SOURCE: Department of Physiology, Zonguldak, Turkey.
 SOURCE: PROSTAGLANDINS LEUKOTRIENES AND ESSENTIAL FATTY
 ACIDS, (2001 Oct) 65 (4) 179-83.
 Journal code: P04; 8802730. ISSN: 0952-3278.
 PUB. COUNTRY: Scotland: United Kingdom
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
 ENTRY DATE: Entered STN: 20011203
 Last Updated on STN: 20011203

AB Oxygen free radicals are implicated in the pathophysiology of ischemia-reperfusion (I/R) injury in skeletal muscle. Nitric oxide (NO) and **prostaglandin E(2)** (PGE(2)) are important regulators of the microcirculation in skeletal muscle. The effects of L-arginine, substrate for NO, and N(G)-nitro L-arginine methyl ester (L-NAME) on PGE(2) synthesis, lipid peroxidation and reduced **glutathione** (GSH) levels was investigated in the rat gastrocnemius muscle after 3 h of reperfusion following 2 h of ischemia. Lipid peroxidation and GSH levels showed a non-significant

changes in the I/R groups compared to the control group. According to these results, it can be assumed that skeletal muscle can resist 2 h of ischemia followed by 3 h of reperfusion-induced oxidative stress. PGE(2)-like activity in the gastrocnemius muscle increased in the L-NAME treated and I/R groups. L-arginine administration reversed the increase in PGE(2)-like activity of reperfused skeletal muscle. These findings support the conclusion that endothelium-derived PGE(2) synthesis increases during reperfusion and suggest that PGE(2) may have a protective role in the maintenance of endothelial function. Copyright 2001 Harcourt Publishers Ltd.

L14 ANSWER 3 OF 28 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001127812 EMBASE

TITLE: Glyceryl trinitrate and acute uterine relaxation: A literature review.

AUTHOR: Caponas G.

CORPORATE SOURCE: Dr. G. Caponas, Nuffield Department of Anaesthetics, John Radcliffe Hospital, Headington, Oxford, United Kingdom. gcaponas@hotmail.com

SOURCE: Anaesthesia and Intensive Care, (2001) 29/2 (163-177).

Refs: 77

ISSN: 0310-057X CODEN: AINCBS

COUNTRY: Australia

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 010 Obstetrics and Gynecology
024 Anesthesiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The use of nitro-vasodilators for achieving rapid uterine relaxation in the resolution of obstetric emergencies has been documented for nearly 120 years. Glyceryltrinitrate (GTN) is the most commonly used nitro-vasodilator for this purpose, with the presumed mechanism of action being via nitric oxide and cyclic guanosine monophosphate (cGMP) mediated processes. GTN is known to release nitric oxide to effect smooth muscle relaxation and some dose response data is available for its vasodilator activity. Human myometrium is known to synthesize and respond to nitric oxide, with changes in the production of and sensitivity to nitric oxide being subject to the cyclical and gestational state of the uterus. Experimental data on the efficacy of GTN in reliably producing uterine relaxation is conflicting and inconsistent. A total of 32 studies and case reports on the use of GTN in achieving rapid uterine relaxation have appeared in the English language literature. Case reports are subject to reporting bias and prospective randomized controlled trials are not without design flaws. Indications for the use of GTN in achieving rapid uterine relaxation cover the antepartum, intrapartum and postpartum periods. The safety of GTN during obstetric emergencies appears high, with no adverse maternal or neonatal outcomes. To establish the efficacy of GTN in reliably achieving uterine relaxation, well designed randomized controlled trials in labouring women are required.

L14 ANSWER 4 OF 28 MEDLINE

09/976805

ACCESSION NUMBER: 2001353754 MEDLINE
DOCUMENT NUMBER: 21111028 PubMed ID: 11178940
TITLE: Tetrahydrobiopterin attenuates modulation of platelet
12-lipoxygenase and cyclooxygenase activities by
nitric oxide.
AUTHOR: Fujimoto Y; Sakuma S; Iba Y; Sasaki T; Fujita T
CORPORATE SOURCE: Department of Hygienic Chemistry, Osaka University of
Pharmaceutical Sciences, 4-20-1 Nasahara, Takatsuki,
Osaka 569-1094, Japan.. fujimoto@oysun01.oups.ac.jp
SOURCE: NITRIC OXIDE, (2001 Feb) 5 (1) 77-81.
Journal code: C5F; 9709307. ISSN: 1089-8603.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010625
Last Updated on STN: 20010625
Entered Medline: 20010621

AB Endothelial cells secrete large amounts of 5,6,7,8-
tetrahydrobiopterin (BH(4)) in septic conditions. BH(4) is a
cofactor for nitric oxide (NO) synthase and an essential regulator
of its activity. We recently showed that NO can be a modulator of
both platelet 12-lipoxygenase and cyclooxygenase activities. In the
present study, we investigated the effect of BH(4) on the activities
of 12-lipoxygenase and cyclooxygenase in rabbit platelets. The
influence of BH(4) on NO-induced modulation of these enzyme
activities was investigated. Exogenous BH(4) did not affect platelet
12-lipoxygenase and cyclooxygenase activities. The modulatory
effects of NO on the two enzymatic pathways were reversed by
addition of BH(4) but not by reduced **glutathione**. These
results suggest that exogenous BH(4) is not essential for NO
synthase activity of platelets, but that it is an important
regulator of the action of NO released from other sources on
platelet 12-lipoxygenase and cyclooxygenase activities. Copyright
2001 Academic Press.

L14 ANSWER 5 OF 28 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001140293 MEDLINE
DOCUMENT NUMBER: 21065356 PubMed ID: 11134359
TITLE: Dual effects of nitric oxide in functional and
regressing rat corpus luteum.
AUTHOR: Motta A B; Estevez A; Tognetti T; Gimeno M A; Franchi
A M
CORPORATE SOURCE: Centro de Estudios Farmacologicos y Botanicos
(CEFYBO), Consejo Nacional de Investigaciones
Cientificas y Tecnicas (CONICET), Serrano 669, 1414
Buenos Aires, Argentina.. amotta@sion.com
SOURCE: MOLECULAR HUMAN REPRODUCTION, (2001 Jan) 7 (1) 43-7.
Journal code: CWO; 9513710. ISSN: 1360-9947.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010308

09/976805

AB The present study investigated the effect of nitric oxide (NO) on the lifespan of the corpus luteum (CL). Using a competitive nitric oxide synthase (NOS) inhibitor, L-nitro arginine methyl ester (L-NAME, 600 micromol/l), and a long-life **NO donor**, diethyl-aminetriamine (DETA-NONOate, 10(-8), 10(-6) or 10(-4) mol/l), we found that in ovaries from rats at the mid stage of CL development, endogenous NO increased both **glutathione** (GSH) and progesterone production. However, during **prostaglandin F(2 alpha)** (PGF(2 alpha))-induced luteolysis NO acted as an intermediary molecule in the inhibitory effect of PGF(2 alpha), on GSH content. This was supported by the fact that in-vivo PGF(2 alpha) treatment enhanced nitric oxide synthase (NOS) activity. These results indicate that the NO could act with a dual action (protective or pro-oxidant) in CL development.

L14 ANSWER 6 OF 28 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-572170 [53] WPIDS
DOC. NO. CPI: C2000-170623
TITLE: New nitrosated and nitrosylated
prostaglandins, useful for treating or
preventing e.g. sexual dysfunction in males and
females, cerebrovascular disorders and glaucoma.
DERWENT CLASS: B05
INVENTOR(S): GARVEY, D S; GASTON, R D; LETTS, G L; SAENZ DE
TEJADA, I; TAM, S W; WORCEL, M
PATENT ASSIGNEE(S): (NITR-N) NITROMED INC
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000051978	A1	20000908	(200053)*	EN	82
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC					
MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM					
EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ					
LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU					
SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000037136	A	20000921	(200065)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000051978	A1	WO 2000-US5286	20000301
AU 2000037136	A	AU 2000-37136	20000301

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000037136	A Based on	WO 200051978

PRIORITY APPLN. INFO: US 1999-138502P 19990609; US 1999-122273P
19990301

AN 2000-572170 [53] WPIDS

AB WO 200051978 A UPAB: 20001023

NOVELTY - Nitrosated and nitrosylated **prostaglandins** (I)

and compositions comprising them are new, also compositions comprising a **prostaglandin** and S-nitrosothiol compound.

DETAILED DESCRIPTION - Nitrosated and nitrosylated **prostaglandins** of formula (I) are new:

bonds a', b', c', d' = single or double bonds;
 R1 = -OD1 or Cl;
 R2, R8 = H; or
 R1+R2 = =CH2 or =O;
 R3, R4 = H, -OD1 or Me;
 R5, R6 = H, -OD1, Me, OMe or -CH=CH2;
 R7 = H or OD1;
 R9 = H or absent when the C to which it is attached is the central carbon of an allene; or
 R8+R9+attached chain atoms = a substituted benzene ring provided that R1 is O which is attached to the C at the position of the benzene ring defined by B';
 A = -CH=, -CH2-, -S- or -O-;
 B' = -CH=, -CH2-, -S- or -C(O)-;
 X = -CH2OR11, -C(O)OR11 or -C(O)N(D1)R12;
 R11 = D1, 1-10C alkyl or a group of formula (i):
 R12 = -S(O)2CH3 or -C(O)CH3;
 Z' = ethyl, butyl, hexyl, benzyl, -CH2-O-CH2-CH3, -CH(CH3)-(CH2)3-CH3 or a group of formula (ii) or (iii):
 R13 = H or Cl;
 D1 = H or D; provided that at least 1 D1 is D;
 D = Q or K;
 Q = -NO or NO2;
 K = -Wa-Eb-(C(Re)(Rf))p-Ec-(C(Re)(Rf))x-Wd
 -(C(Re)(Rf))y-Wi-Ej-Wg-(C(Re)(Rf))z-T-Q;
 a, b, c, d, g, i, j = 0-3;
 p, x, y, z = 0-10;
 E = -T-, alkyl, aryl, (C(Re)(Rf))h-,
 W = -C(O)-, -C(S)- or as defined for E;
 h = 1-10;
 q = 1-5;
 Re, Rf = H, alkyl, cycloalkoxy, halo, OH, hydroxyalkyl, alkoxyalkyl, aryl-heterocyclic, alkylaryl, cycloalkylalkyl, heterocyclic-alkyl, alkoxy, haloalkoxy, NH2, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkoxyhaloalkyl, haloalkoxy, sulfonic acid, sulfonic ester, alkylsulfonic acid, arylsulfonic acid, arylalkoxy, alkylthio, arylthio, cycloalkylthio, cycloalkenyl, CN, aminoalkyl, aminoaryl, aryl, arylalkyl, alkylaryl, carboxamido, alkylcarboxamido, arylcarboxamido, amidyl, carboxyl, carbamoyl, alkylcarboxylic acid, arylcarboxylic acid, alkylcarbonyl, arylcarbonyl, ester, carboxylic ester, alkylcarboxylic ester, arylcarboxylic ester, haloalkoxy, sulfonamido, alkylsulfonamido, arylsulfonamido, sulfonic ester, a urea, phosphoryl, nitro, -T-Q or -(C(Re)(Rf))k-T-Q; or
 Re+Rf+attached C atoms = carbonyl, methanthial, heterocyclic, cycloalkyl or a bridged cycloalkyl;
 k = 1-3;
 T = a covalent bond, carbonyl, O, -S(O)o- or -N(Ra)Ri-;
 o = 0-2;
 Ra = a lone pair of electrons, H or alkyl;
 Ri = H, alkyl, aryl, alkylcarboxylic acid, arylcarboxylic acid, alkylcarboxylic ester, arylcarboxylic ester, alkylcarboxamido, arylcarboxamido, alkylaryl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, sulfonamido, carboxamido, carboxylic

ester, amino alkyl, amino aryl, $-\text{CH}_2-\text{C}(\text{T}-\text{Q})(\text{Re})(\text{Rf})$ or $-(\text{N}_2\text{O}_2)-\text{M}^+$;

M^+ = an organic or inorganic cation;

provided that when R_i is $-\text{CH}_2-\text{C}(\text{T}-\text{Q})(\text{Re})(\text{Rf})$ or $-(\text{N}_2\text{O}_2)-\text{M}^+$; or Re or Rf are $\text{T}-\text{Q}$ or $(\text{C}(\text{Re})(\text{Rf}))_k-\text{T}-\text{Q}$, then $\text{T}-\text{Q}$ can be H , alkyl, alkoxy, alkoxyalkyl, aminoalkyl, OH , heterocyclic or aryl; and provided that when X is $-\text{C}(\text{O})\text{ODl}$ and Dl is K , then K is not alkyl or cycloalkyl mononitrate; benzoic acid substituted benzyloxy mononitrate; ethylene glycol mononitrate; polyethylene glycol mononitrate; the regioisomeric esters of glycerol dinitrate and oligomers as disclosed in WO9858910.

INDEPENDENT CLAIMS are included for the following:

(a) compositions and kits comprising (I) and at least 1 compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase, and/or at least 1 vasoactive agent; and

(b) compositions and kits comprising at least 1 prostaglandin and at least 1 S-nitrosothiol compound, useful for treating sexual dysfunction, a cerebrovascular disorder, cardiovascular disorder, benign prostatic hyperplasia, organ transplants, glaucoma or peptic ulcer, or for inducing an abortion.

ACTIVITY - Vasotropic; Cerebroprotective; Cardiant; Cytostatic; Ophthalmological; Antiulcer; Gynecological; Relaxant.

MECHANISM OF ACTION - Smooth muscle relaxant; Nitric oxide donor; Endothelium-derived relaxing factor agonist.

USE - For treating or preventing sexual dysfunction in males or females, treating a cerebrovascular disorder, cardiovascular disorder, benign prostatic hyperplasia, organ transplants, glaucoma or peptic ulcer, or for inducing an abortion (all claimed).

ADVANTAGE - The combination of a prostaglandin and a S-nitrosothiol gives synergistic results.

Dwg.0/4

L14 ANSWER 7 OF 28 MEDLINE
 ACCESSION NUMBER: 2001028875 MEDLINE
 DOCUMENT NUMBER: 20501168 PubMed ID: 11046092
 TITLE: Rationale for the combination of **PGE** (1) and S-nitroso-**glutathione** to induce relaxation of human penile smooth muscle.
 AUTHOR: Angulo J; Cuevas P; Moncada I; Martin-Morales A; Allona A; Fernandez A; Gabancho S; Ney P; Saenz de Tejada I
 CORPORATE SOURCE: Fundacion para la Investigacion y el Desarrollo en Andrologia, Madrid, Spain.
 SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2000 Nov) 295 (2) 586-93.
 Journal code: JP3. ISSN: 0022-3565.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200011
 ENTRY DATE: Entered STN: 20010322
 Last Updated on STN: 20010322
 Entered Medline: 20001121
 AB Many men with erectile dysfunction have been successfully treated with intracavernosal injection of **prostaglandin E**(1) (**PGE**(1)) but this treatment is ineffective in 30 to

40% of patients. The goals of this study were to characterize PGE(1)-induced relaxation of isolated human penile smooth muscle (penile arteries and trabecular strips), correlating this in vitro response with the clinical response to this drug, and to evaluate the effects of the combination of PGE(1) with S-nitrosoglutathione (SNO-Glu) on relaxation of isolated human penile smooth muscle. Large variability in the EC(50) and maximal relaxation induced by PGE(1) was observed between tissues of different patients. Patients with poor clinical response to intracavernosal alprostadil (PGE(1)) had significantly larger EC(50) values and smaller maximal relaxation compared with patients with partial or complete clinical response to this drug. SNO-Glu consistently produced complete or near complete relaxation of human corpus cavernosum strips and penile arteries, even when the tissue responded poorly to PGE(1). In trabecular strips, the combination of PGE(1) and SNO-Glu in a 1:100 ratio demonstrated a synergistic relaxation effect. The combination of PGE(1) and SNO-Glu simultaneously increased the levels of both cAMP and cGMP in human corpus cavernosum tissue. Our results suggest that the clinical effectiveness of intracavernosal administration of PGE(1) is related to the variability of the relaxation responses of human trabecular tissue and penile arteries to this drug. The synergistic interaction of PGE(1) and SNO-Glu makes this combination an effective method to cause penile smooth muscle relaxation, a necessary step to initiate and maintain penile erection.

L14 ANSWER 8 OF 28 MEDLINE
 ACCESSION NUMBER: 1999135884 MEDLINE
 DOCUMENT NUMBER: 99135884 PubMed ID: 9950682
 TITLE: NF-kappaB and AP-1 activation by nitric oxide attenuated apoptotic cell death in RAW 264.7 macrophages.
 AUTHOR: von Knethen A; Callsen D; Brune B
 CORPORATE SOURCE: University of Erlangen-Nurnberg, Faculty of Medicine, Department of Medicine IV-Experimental Division, Erlangen, Germany.
 SOURCE: MOLECULAR BIOLOGY OF THE CELL, (1999 Feb) 10 (2) 361-72.
 Journal code: BAU; 9201390. ISSN: 1059-1524.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199903
 ENTRY DATE: Entered STN: 19990326
 Last Updated on STN: 19990326
 Entered Medline: 19990318
 AB A toxic dose of the nitric oxide (NO) donor S-nitrosoglutathione (GSNO; 1 mM) promoted apoptotic cell death of RAW 264.7 macrophages, which was attenuated by cellular preactivation with a nontoxic dose of GSNO (200 microM) or with lipopolysaccharide, interferon-gamma, and NG-monomethyl-L-arginine (LPS/IFN-gamma/NMMA) for 15 h. Protection from apoptosis was achieved by expression of cyclooxygenase-2 (Cox-2). Here we investigated the underlying mechanisms leading to Cox-2 expression. LPS/IFN-gamma/NMMA prestimulation activated nuclear factor

(NF)-kappaB and promoted Cox-2 expression. Cox-2 induction by low-dose GSNO demanded activation of both NF-kappaB and activator protein-1 (AP-1). NF-kappaB supershift analysis implied an active p50/p65 heterodimer, and a luciferase reporter construct, containing four copies of the NF-kappaB site derived from the murine Cox-2 promoter, confirmed NF-kappaB activation after NO addition. An NF-kappaB decoy approach abrogated not only Cox-2 expression after low-dose NO or after LPS/IFN-gamma/NMMA but also inducible protection. The importance of AP-1 for Cox-2 expression and cell protection by low-level NO was substantiated by using the extracellular signal-regulated kinase inhibitor PD98059, blocking NO-elicited Cox-2 expression, but leaving the cytokine signal unaltered. Transient transfection of a dominant-negative c-Jun mutant further attenuated Cox-2 expression by low-level NO. Whereas cytokine-mediated Cox-2 induction relies on NF-kappaB activation, a low-level NO-elicited Cox-2 response required activation of both NF-kappaB and AP-1.

L14 ANSWER 9 OF 28 SCISEARCH COPYRIGHT 2001 ISI (R)
 ACCESSION NUMBER: 1999:361043 SCISEARCH
 THE GENUINE ARTICLE: 192UF
 TITLE: Cross-talk between group IIA-phospholipase A(2) and inducible NO-synthase in rat renal mesangial cells
 AUTHOR: Rupprecht G; Scholz K; Beck K F; Geiger H; Pfeilschifter J; Kaszkin M (Reprint)
 CORPORATE SOURCE: KLINIKUM JOHANN WOLFGANG GOETHE UNIV, MED KLIN 4, FUNKT BEREICH NEPHROL, THEODOR STERN KAI 7, D-60590 FRANKFURT, GERMANY (Reprint); KLINIKUM JOHANN WOLFGANG GOETHE UNIV, MED KLIN 4, FUNKT BEREICH NEPHROL, D-60590 FRANKFURT, GERMANY; KLINIKUM JOHANN WOLFGANG GOETHE UNIV, ZENTRUM PHARMAKOL, D-60590 FRANKFURT, GERMANY
 COUNTRY OF AUTHOR: GERMANY
 SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (MAY 1999) Vol. 127, No. 1, pp. 51-56.
 Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND.
 ISSN: 0007-1188.
 DOCUMENT TYPE: Article; Journal
 FILE SEGMENT: LIFE
 LANGUAGE: English
 REFERENCE COUNT: 40

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB 1 Features of glomerulonephritis are expression of the inducible form of NO synthase (iNOS) as well as expression of the secretory group IIA-phospholipase A(2) (sPLA(2)) in mesangial cells. Interleukin 1 beta (IL-1 beta) induces both enzymes with a similar time course resulting in an increase in nitrite production and sPLA(2)-IIA activity. In this study we investigated the relationship between the formation of NO and sPLA(2)-IIA induction in rat renal mesangial cells.

2 Incubation of mesangial cells with the NO-donor, spermine-NONOate, for 24 h induced sPLA(2)-IIA mRNA expression and activity, whereas S-nitroso glutathione alone had only a small stimulatory effect. Stimulation of cells with IL-1B caused a marked increase in sPLA(2)-IIA mRNA and activity that were potentiated 3 fold by both NO donors.

3 Coincubation of cells with IL-1 beta and the NOS inhibitor,

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L-N-G monomethylarginine (L-NMMA), caused a dose-dependent inhibition of cytokine-induced sPLA(2)-IIA mRNA expression and activity.

4 sPLA(2)-IIA activity was not stimulated by 8-bromo-cyclic GMP indicating that NO-induced sPLA(2)-IIA induction is independent of cyclic GMP-mediated signal transduction.

5 These data show that NO contributes to the expression by cytokines of sPLA(2)-IIA and establishes a novel type of interaction between iNOS and sPLA(2)-IIA in mesangial cells. This cross-talk between inflammatory mediators may help to promote and sustain an inflammatory state in the kidney.

L14 ANSWER 10 OF 28 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1998452995 MEDLINE
DOCUMENT NUMBER: 98452995 PubMed ID: 9781735
TITLE: Effects of vasoactive drugs on gastric intramucosal pH.
COMMENT: Comment in: Crit Care Med. 1998 Oct;26(10):1637-8
Comment in: Crit Care Med. 1999 Dec;27(12):2848
AUTHOR: Silva E; DeBacker D; Creteur J; Vincent J L
CORPORATE SOURCE: Department of Intensive Care Medicine, Erasme University Hospital, Free University of Brussels, Belgium.
SOURCE: CRITICAL CARE MEDICINE, (1998 Oct) 26 (10) 1749-58.
Ref: 98
Journal code: DTF; 0355501. ISSN: 0090-3493.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 20000512
Entered Medline: 19981105
AB OBJECTIVE: To review current knowledge about the effects of vasoactive agents on gastric intramucosal pH (pHi). DATA SOURCES: All studies involving pHi and vasoactive agents were retrieved from a computerized MEDLINE search from 1980 to 1997. We also reviewed the reference lists of all available review articles and primary studies to identify references not found in the computerized searches. STUDY SELECTION: Clinical and experimental studies using dopamine, dopexamine, dobutamine, norepinephrine, epinephrine, nitric oxide, N-acetylcysteine, prostaglandins, or pentoxifylline were considered if splanchnic perfusion and/or pHi measurements were utilized. DATA EXTRACTION: From the selected studies, information was obtained regarding patient population, dosing regimen, duration of study, and effects on splanchnic blood flow (SBF), splanchnic oxygenation, and pHi. DATA SYNTHESIS: Although dopaminergic effects increase SBF, dopamine does not generally increase pHi. Data on the effects of dopexamine on pHi are scarce and inconsistent. Dobutamine can significantly increase SBF and usually increases pHi. In septic patients, norepinephrine seems to increase pHi. Epinephrine may have detrimental effects on gastric perfusion. Prostacyclin seems to increase pHi but data are limited. Insufficient evidence exists to support the beneficial effects of nitric oxide donors or blockers,

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pentoxifylline, or **N-acetylcysteine** on pHi. CONCLUSIONS:
Overall, the effects of vasoactive agents on pHi are unpredictable.
Among the catecholamines, dopamine is the least likely, and
dobutamine the most likely, to increase pHi.

L14 ANSWER 11 OF 28 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1998289938 MEDLINE
DOCUMENT NUMBER: 98289938 PubMed ID: 9626636
TITLE: Role of nitric oxide and **prostaglandins** in
mechanically induced bone formation.
AUTHOR: Chow J W; Fox S W; Lean J M; Chambers T J
CORPORATE SOURCE: Department of Histopathology, St. George's Hospital
Medical School, London, United Kingdom.
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (1998 Jun) 13
(6) 1039-44.
Journal code: 130; 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981029
Last Updated on STN: 19981029
Entered Medline: 19981022

AB We have previously shown that **prostaglandins** (PG) and
nitric oxide (NO) are required in the induction of bone formation by
mechanical stimulation. We therefore tested the ability of
NO donors, S-nitroso-N-acetyl-D,L-penicillamine
(SNAP), and S-nitroso-**glutathione** (GSNO) to mimic or
augment the osteogenic response of bone to a minimal mechanical
stimulus. In rats administered vehicle or the vasodilator
hydralazine, stimulation of the 8th caudal vertebra increased bone
formation. In animals treated with SNAP or GSNO, there was
significant potentiation of this osteogenic response. The bone
formation rate in nonloaded vertebrae was unaffected by
administration of the **NO donors**. We also found
that while inhibition of either PG or NO production at the time of
loading caused a partial suppression of c-fos mRNA expression in the
loaded vertebrae, administration of indomethacin and
NG-monomethyl-L-arginine together markedly suppressed c-fos
expression. This suggests that although both PG and NO are required
in mechanically induced osteogenesis, they appear to be generated
largely independently of each other. Moreover, while exogenous NO
potentiates the stimulatory effect of mechanical loading on bone
formation, the lack of effect in nonloaded vertebrae suggests that
NO is necessary but not sufficient for induction of bone formation.

L14 ANSWER 12 OF 28 MEDLINE
ACCESSION NUMBER: 1999023667 MEDLINE
DOCUMENT NUMBER: 99023667 PubMed ID: 9808481
TITLE: The **nitric oxide donor**
sodium nitroprusside is protective in
ischemia/reperfusion injury of the pancreas.
AUTHOR: Benz S; Schnabel R; Weber H; Pfeffer F; Wiesner R;
von Breitenbuch P; Nizze H; Schareck W; Hopt U T
CORPORATE SOURCE: Department of Surgery, University of Rostock,
Germany.
SOURCE: TRANSPLANTATION, (1998 Oct 27) 66 (8) 994-9.

Searcher : Shears 308-4994

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JOURNAL code: WEJ; 0132144. ISSN: 0041-1337.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981125

AB BACKGROUND: The role of nitric oxide in the ischemia/reperfusion injury of the pancreas is still unclear. In other organs, protective as well as aggravating effects have been described. We have, therefore, investigated the effect of the **nitric oxide donor** sodium nitroprusside on pancreatic ischemia/reperfusion injury. METHODS: In Landrace pigs, after transection of the pancreas, complete vascular isolation of the pancreatic tail was performed. The tail was subjected to 3 hr of warm ischemia and thereafter reperfusion (6 hr). The animals were divided into a control group (n=7) and a treatment group (n=7) that received 15 mg of sodium nitroprusside after reperfusion intra-arterially into the splenic artery. RESULTS: The morphological tissue damage and lipase activity in the venous effluent of the pancreas were significantly lower in the treatment group. Partial oxygen tension in the tissue after reperfusion was markedly reduced in the control group, indicating an impairment of microcirculation. In the treatment group, however, partial oxygen tension in the tissue was significantly higher (43 vs. 20 mmHg; P<0.014). Furthermore, total blood flow through the pancreatic tail in the treatment group was found to be significantly higher in the late reperfusion period (14 vs. 9.5 ml/min at 5 hr after reperfusion; P<0.05). CONCLUSION: There is a marked impairment of pancreatic microcirculation after reperfusion. Sodium nitroprusside counteracts this impairment and has a protective effect on ischemia/reperfusion injury of the pancreas.

L14 ANSWER 13 OF 28 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998149263 MEDLINE
DOCUMENT NUMBER: 98149263 PubMed ID: 9489619
TITLE: Characterization of NS 2028 as a specific inhibitor of soluble guanylyl cyclase.
AUTHOR: Olesen S P; Drejer J; Axelsson O; Moldt P; Bang L; Nielsen-Kudsk J E; Busse R; Mulsch A
CORPORATE SOURCE: NeuroSearch, Glostrup, Denmark.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1998 Jan) 123 (2) 299-309.
Journal code: B00; 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980422
Last Updated on STN: 19980422
Entered Medline: 19980414

AB 1 The haeme-containing soluble guanylyl cyclase (alpha1beta1-heterodimer) is a major intracellular receptor and effector for nitric oxide (NO) and carbon monoxide (CO) and mediates many of their biological actions by increasing cyclic GMP. We have

synthesized new oxadiazolo-benz-oxazins and have assessed their inhibitory actions on guanylyl cyclase activity in vitro, on the formation of cyclic GMP in cultured cells and on the NO-dependent relaxation of vascular and non-vascular smooth muscle. 2 Soluble guanylyl cyclase, purified to homogeneity from bovine lung, was inhibited by 4H-8-bromo-1,2,4-oxadiazolo(3,4-d)benz(b)(1,4)oxazin-1-one (NS 2028) in a concentration-dependent and irreversible manner (IC₅₀ 30 nM for basal and 200 nM for NO-stimulated enzyme activity). Evaluation of the inhibition kinetics according to Kitz & Wilson yielded a value of 8 nM for K_i, the equilibrium constant describing the initial reversible reaction between inhibitor and enzyme, and 0.2 min⁻¹ for the rate constant k₃ of the subsequent irreversible inhibition. Inhibition was accompanied by a shift in the sorbet absorption maximum of the enzyme's haem cofactor from 430 to 390 nm. 3 S-nitroso-glutathione-enhanced soluble guanylyl cyclase activity in homogenates of mouse cerebellum was inhibited by NS 2028 (IC₅₀ 17 nM) and by 17 structural analogues in a similar manner, albeit with different potency, depending on the type of substitution at positions 1, 7 and 8 of the benzoxazin structure. Small electronegative ligands such as Br and Cl at position 7 or 8 increased and substitution of the oxygen at position 1 by -S-, -NH- or -CH₂- decreased the inhibition. 4 In tissue slices prepared from mouse cerebellum, neuronal NO synthase-dependent activation of soluble guanylyl cyclase by the glutamate receptor agonist N-methyl-D-aspartate was inhibited by NS 2028 (IC₅₀ 20 nM) and by two of its analogues. Similarly, 3-morpholino-sydnominine (SIN-1)-elicited formation of cyclic GMP in human cultured umbilical vein endothelial cells was inhibited by NS 2028 (IC₅₀ 30 nM). 5 In prostaglandin F₂α-constricted, endothelium-intact porcine coronary arteries NS 2028 elicited a concentration-dependent increase (65%) in contractile tone (EC₅₀ 170 nM), which was abolished by removal of the endothelium. NS 2028 (1 microM) suppressed the relaxant response to **nitroglycerin** from 88.3±2.1 to 26.8±6.4% and induced a 9 fold rightward shift (EC₅₀ 15 microM) of the concentration-relaxation response curve to **nitroglycerin**. It abolished the relaxation to sodium nitroprusside (1 microM), but did not affect the vasorelaxation to the KATP channel opener cromakalim. Approximately 50% of the relaxant response to sodium nitroprusside was recovered after 2 h washout of NS 2028. 6 In phenylephrine-precontracted, endothelium-denuded aorta of the rabbit NS 2028 (1 microM) did not affect relaxant responses to atrial natriuretic factor, an activator of particulate guanylyl cyclase, or forskolin, an activator of adenylyl cyclase. 7 NO-dependent relaxant responses in non-vascular smooth muscle were also inhibited by NS 2028. The **nitroglycerin**-induced relaxation of guinea-pig trachea precontracted by histamine was fully inhibited by NS 2028 (1 microM), whereas the relaxations to terbutaline, theophylline and vasoactive intestinal polypeptide (VIP) were not affected. The relaxant responses to electrical field stimulation of non-adrenergic, non-cholinergic nerves in the same tissue were attenuated by 50% in the presence of NS 2028 (1 microM). 8 NS 2028 and its analogues, one of which is the previously characterized 1H-[1,2,4]oxadiazolo[4,3,-a]quinoxalin-1-one (ODQ), appear to be potent and specific inhibitors of soluble guanylyl cyclase present in various cell types. Oxidation and/or a change in the coordination of the haeme-iron of guanylyl cyclase is a likely inhibitory mechanism.

L14 ANSWER 14 OF 28 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1998:154941 BIOSIS

DOCUMENT NUMBER: PREV199800154941

TITLE: The role of nitric oxide and **prostaglandins** in mechanically-induced bone formation.

AUTHOR(S): Chow, J. W. M.; Fox, S.; Lean, J. M.; Chambers, T. J.

CORPORATE SOURCE: St. George's Hosp. Med. Sch., London UK

SOURCE: Journal of Pathology, (1998) Vol. 184, No. SUPPL., pp. 12A.
Meeting Info.: 176th Meeting of the Pathological Society of Great Britain and Ireland London, England, UK January 7-9, 1998 Departments of Histopathology and Medical Microbiology, Imperial College School of Medicine at Charing Cross, London
. ISSN: 0022-3417.

DOCUMENT TYPE: Conference

LANGUAGE: English

L14 ANSWER 15 OF 28 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 5

ACCESSION NUMBER: 1996:235432 BIOSIS

DOCUMENT NUMBER: PREV199698799561

TITLE: Effective 30-hour preservation of canine lungs with modified ET-Kyoto solution.

AUTHOR(S): Wada, Hiromi (1); Liu, Chun Jiang; Hirata, Toshiki; Bando, Toru; Kosaka, Shinji

CORPORATE SOURCE: (1) Dep. Thoracic Surgery, Chest Disease Res. Inst., Kyoto Univ., Kawaharacho 53, Shogo-in, Sakyo-ku, Kyoto 606 Japan

SOURCE: Annals of Thoracic Surgery, (1996) Vol. 61, No. 4, pp. 1099-1105.
ISSN: 0003-4975.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Background: With the aim of developing a preservation solution that can preserve donor lungs reliably for a long time, we prepared a modified ET-Kyoto solution by adding **N-acetylcysteine**, **nitroglycerin**, and dibutyladenosin 3',5'-cyclic phosphate to the previously reported ET-Kyoto solution, which contains trehalose, gluconate, and hydroxyethyl starch. In this study, we examined the efficacy of modified ET-Kyoto solution in 30 hour lung preservation. Methods: Twenty-five pairs of adult mongrel dogs were divided into four groups. Donor lungs were flushed with modified ET-Kyoto solution (n = 9), with ET-Kyoto solution (n = 6), with University of Wisconsin solution group (n = 6), or with ET-Kyoto solution plus the solvents of **nitroglycerin** (ethanol and propylene glycol) (n = 4), then stored at 4 degree C for 30 hours. All animals were treated with **prostaglandin E-1**. Left lungs were transplanted and reperused for 6 hours. Results: With respect to arterial oxygen tension, peak inspiratory pressure, and wet-to-dry lung weight ratio, modified ET-Kyoto solution was significantly superior to ET-Kyoto solution. The modified ET-Kyoto solution was significantly superior to University of Wisconsin solution with respect to survival rate, arterial oxygen tension, and wet-to-dry lung weight ratio. Ultrastructural findings supported these results. Conclusions: These results suggest that modified ET-Kyoto solution is superior to University of Wisconsin solution for 30-hour lung preservation.

L14 ANSWER 16 OF 28 MEDLINE DUPLICATE 6
 ACCESSION NUMBER: 97081503 MEDLINE
 DOCUMENT NUMBER: 97081503 PubMed ID: 8922746
 TITLE: Endothelium-derived factors and hyperpolarization of the carotid artery of the guinea-pig.
 AUTHOR: Corriu C; Feletou M; Canet E; Vanhoutte P M
 CORPORATE SOURCE: Departement de pneumologie, Institut de Recherches Servier, Suresnes, France.
 SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1996 Nov) 119 (5) 959-64.
 Journal code: B00; 7502536. ISSN: 0007-1188.
 PUB. COUNTRY: ENGLAND: United Kingdom
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199703
 ENTRY DATE: Entered STN: 19970321
 Last Updated on STN: 19970321
 Entered Medline: 19970310

AB 1. Transmembrane potentials were recorded from isolated carotid arteries of the guinea-pig superfused with modified Krebs-Ringer bicarbonate solution. Smooth muscle cells were impaled from the adventitial side with intracellular glass microelectrodes filled with KCl (30-80 M omega). 2. Acetylcholine (1 microM) in the presence of inhibitors of nitric oxide synthase, (N omega-nitro-L-arginine (L-NOARG) 100 microM) and cyclo-oxygenase, (indomethacin 5 microM) induced an endothelium-dependent hyperpolarization (-18.9 +/- 1.6 mV, n = 15). 3. In the presence of these two inhibitors, S-nitroso-L-glutathione (10 microM), sodium nitroprusside (10 microM), 3-morpholinolinosydnonimine (SIN-1, 10 microM) and iloprost (0.1 microM) induced endothelium-independent hyperpolarizations of the smooth muscle cells (respectively: -16.0 +/- 2.3, -16.3 +/- 3.4, -12.8 +/- 2.0 and -14.5 +/- 1.5 mV, n = 4-6). 4. The addition of glibenclamide (1 microM) did not influence the acetylcholine-induced L-NOARG/ indomethacin-resistant hyperpolarization (-18.0 +/- 1.8 mV, n = 10). In contrast, the responses induced by S-nitroso-L-glutathione, sodium nitroprusside, SIN-1 and iloprost were abolished (changes in membrane potential: -0.8 +/- 1.1, 1.3 +/- 3.9, 4.5 +/- 4.6 and 0.3 +/- 0.8 mV respectively, n = 4-5). 5. In the presence of NO synthase and cyclo-oxygenase inhibitors, charybdotoxin (0.1 microM) or apamin (0.5 microM) did not influence the hyperpolarization produced by acetylcholine. However, in the presence of the combination of charybdotoxin and apamin, the acetylcholine-induced L-NOARG/indomethacin-resistant hyperpolarization was converted to a depolarization (4.4 +/- 1.2 mV, n = 20) while the endothelium-independent hyperpolarizations induced by S-nitroso-L-glutathione, sodium nitroprusside, SIN-1 and iloprost were not affected significantly (respectively: -20.4 +/- 3.4, -22.5 +/- 4.9, -14.5 +/- 4.7 and -14.5 +/- 0.5 mV, n = 4-5). 6. In the presence of the combination of charybdotoxin and apamin and in the absence of L-NOARG and indomethacin, acetylcholine induced a hyperpolarization (-19.5 +/- 3.7 mV, n = 4). This hyperpolarization induced by acetylcholine was not affected by the addition of indomethacin (-18.3 +/- 4.6 mV, n = 3). In the presence of the combination of charybdotoxin, apamin and L-NOARG (in the absence of indomethacin), acetylcholine, in 5 out of 7 vessels, still produced

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hyperpolarization which was not significantly smaller (-9.1 ± 5.6 mV, $n = 7$) than the one observed in the absence of L-NOARG. 7. These findings suggest that, in the guinea-pig isolated carotid artery, the endothelium-independent hyperpolarizations induced by **NO donors** and iloprost involve the opening of KATP channels while the acetylcholine-induced endothelium-dependent hyperpolarization (resistant to the inhibition of NO-synthase and cyclo-oxygenase) involves the opening of Ca(2+)-activated potassium channel(s). Furthermore, in this tissue, acetylcholine induces the simultaneous release of various factors from endothelial origin: hyperpolarizing factors (NO, endothelium derived hyperpolarizing factor (EDHF) and **prostaglandins**) and possibly a depolarizing factor.

L14 ANSWER 17 OF 28 MEDLINE
ACCESSION NUMBER: 97159998 MEDLINE
DOCUMENT NUMBER: 97159998 PubMed ID: 9007514
TITLE: Heterogeneity of glyceryl trinitrate response in isolated bovine coronary arteries.
AUTHOR: De la Lande I S; Stafford I; Horowitz J D
CORPORATE SOURCE: Cardiology Unit, Queen Elizabeth Hospital, University of Adelaide, Australia.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1996 Dec 27) 318 (1) 65-71.
JOURNAL CODE: EN6; 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
JOURNAL; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970523
Last Updated on STN: 19980206
Entered Medline: 19970515

AB Factors determining heterogeneity of response to glyceryl trinitrate in coronary microvessels have been extensively documented in recent years, but determinants of heterogeneity between conduit and large resistance vessels are poorly understood. The current study has characterised heterogeneity to glyceryl trinitrate and other vasodilators in bovine isolated proximal (4.5 mm i.d.) and distal (0.5 mm i.d.) segments of left anterior descending artery. Compared with proximal segments, distal segments were less responsive to glyceryl trinitrate and sodium nitroprusside, equi-responsive to S-nitroso-N-acetylpenicillamine, and more responsive to isoprenaline. Heterogeneity to glyceryl trinitrate was unaffected by the presence of the thiols (cysteine or N-acetylcysteine, 100 microM). The results are interpreted as evidence that heterogeneity of vascular responsiveness to glyceryl trinitrate reflects impairment in the small artery of the cellular events which precede activation of the cyclic GMP pathway. An implication is that the impairment is not a consequence of limited thiol availability, and in this respect the cellular mechanism of heterogeneity differs from those proposed for the coronary microvasculature.

L14 ANSWER 18 OF 28 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 7
ACCESSION NUMBER: 1991:207424 BIOSIS
DOCUMENT NUMBER: BA91:110649
TITLE: CAPTOPRIL-INDUCED REVERSAL OF NITROGLYCERIN TOLERANCE ROLE OF SULFHYDRYL GROUP VERSUS

09/976805

ACE-INHIBITORY ACTIVITY.
AUTHOR(S): LAWSON D L; NICHOLS W W; MEHTA P; MEHTA J L
CORPORATE SOURCE: DEP. MED., BOX J-277, JHMC, UNIV. FLORIDA,
GAINESVILLE, FLA. 32610.
SOURCE: J CARDIOVASC PHARMACOL, (1991) 17 (3), 411-418.
CODEN: JPCPDT. ISSN: 0160-2446.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The angiotensin-converting enzyme (ACE) inhibitor captopril has been shown to reverse vascular tolerance to **nitroglycerin** (**NTG**). Whether captopril reverses **NTG** tolerance by providing sulfhydryl (SH) groups or by inhibiting ACE is not clear. To examine this issue, we treated rat aortic rings with buffer, captopril (SH+, ACE inhibitory activity+), enalaprilat (SH-, ACE inhibitory activity+), or N-**acetylcysteine** (**NAC**, SH+, ACE inhibitory activity-) prior to their contraction with epinephrine and subsequent relaxation with **NTG**. Previous exposure of **NTG**-treated rings resulted in marked resistance to the vasorelaxant effect of a subsequent exposure to **NTG** in buffer-treated rings. Both **NAC** and captopril, but not enalaprilat, potentiated the vasorelaxant effects of **NTG** during the first exposure of vascular rings to **NTG** and also prevented the development of tolerance of **NTG** during a second exposure. Buffer-treated rings showed an inability to accumulate cyclic guanosine monophosphate (GMP) in response to a second exposure to **NTG**. In contrast, both **NAC** and captopril-pretreated rings demonstrated a persistence of cyclic GMP accumulation during the second **NTG** exposure. The endothelium-dependent vasodilator acetylcholine (ACh) caused relaxation of the **NTG**-tolerant rings and also induced cyclic GMP accumulation in these rings. In other experiments, we found that prior exposure of vascular rings to ACh did not cause resistance to the subsequent vasorelaxant effects of ACh. **NAC**, captopril, and enalaprilat did not modulate the effects of ACh during either the first or subsequent exposures of ACh. In addition, indomethacin did not influence the "protective" effects of **NAC** or captopril against **NTG** tolerance. These data show that **NTG** tolerance does not cause cross-tolerance to ACh. The availability of the SH group, as in **NAC** and captopril, and not the ACE-inhibitory activity alone, as in enalaprilat, modifies **NTG** tolerance, and these effects of **NAC** or captopril are not modified by **prostaglandin** inhibition. Lastly, these agents do not modulate the vasorelaxant effects of ACh.

L14 ANSWER 19 OF 28 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91316653 EMBASE
DOCUMENT NUMBER: 1991316653
TITLE: [Vasodilator drugs that act stimulating guanylate cyclase of vascular smooth muscle].
REVISION DE TEMAS CARDIOLOGICOS. FARMACOS VASODILADORES QUE ACTUAN ESTIMULANDO A LA GUANILATO CICLASA EN EL MUSCULO LISO VASCULAR.
AUTHOR: Castillo C.; Hong E.
CORPORATE SOURCE: Seccion de Terapeutica Experimental, Departamento de Farmacologia y Toxicologia, Centro de Investigacion, Estudios Avanzados, Instituto Politecnico Nacional de Mexico, Mexico

09/976805

SOURCE: Archivos del Instituto de Cardiologia de Mexico,
(1991) 61/4 (375-384).
ISSN: 0020-3785 CODEN: AICMA2
COUNTRY: Mexico
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular
Surgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

LANGUAGE: Spanish

SUMMARY LANGUAGE: Spanish; English; French

AB Many exogenous and endogenous vasodilator substances produce their effects by stimulation of guanylate cyclase in vascular smooth muscle and increasing cyclic 3',5' - guanosin monophosphate (cGMP) levels. Activation of such enzyme leads to vasodilatation. Possibly as a consequence of a change in the pattern of protein phosphorylation, including dephosphorylation of the light chain myosin and of a decrease in the bioavailability of free calcium. Guanylate cyclase exists in two different forms in the vascular smooth muscle cells: a cytosolic (soluble) and the other associated to membranes (particulate). The nitrovasodilators and vasodilators with endothelium dependent activity, act by main stimulation of the soluble guanylate cyclase, while the atrial natriuretic factor acts specifically on the particulate form of the enzyme. Guanylate cyclase represents the final path in the vasodilation induced by diverse endogenous and exogenous substances; an aspect that has created a great interest among investigators due to its possible physiological, physiopathological and therapeutic implications. The more relevant aspects related with the mechanism of action of this numerous group of drugs are deeply analyzed in the present review.

L14 ANSWER 20 OF 28 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 92208122 EMBASE

DOCUMENT NUMBER: 1992208122

TITLE: [Nitrate derivatives in anaesthesia and
resuscitation: Physiopathologic basis and therapeutic
indications].

DERIVES NITRES ET ANESTHESIE-REANIMATION: BASES
PHYSIOPATHOLOGIQUES ET INDICATIONS THERAPEUTIQUES.

AUTHOR: Beloucif S.; Beloucif L.; Payen D.

CORPORATE SOURCE: Departement d'Anesthesie-Reanimation, Hopital
Lariboisiere, 2, Rue Ambroise-Pare, 75010 Paris,
France

SOURCE: Cahiers d'Anesthesiologie, (1991) 39/4 (261-274).

ISSN: 0079-7625 CODEN: CAANBU

COUNTRY: France

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 002 Physiology
006 Internal Medicine
009 Surgery
018 Cardiovascular Diseases and Cardiovascular
Surgery
024 Anesthesiology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

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038 Adverse Reactions Titles

LANGUAGE: French

SUMMARY LANGUAGE: English; French

AB This review briefly describes the cellular mechanisms of nitrates and the tolerance. Nitrates activate NO production thus GMPc in the smooth muscle cell explaining their vasodilating properties even in absence of an intact endothelium. The biologic pathway of AMPc is stimulated by prostaglandin activated by nitrates. Tolerance to these agents could result from depletion of sulfhydryl radical but also from reflex cardiovascular adaptation. After a brief recall of pharmacokinetic, pharmacodynamic properties are detailed. Therapeutic use in cardiac surgery, non-cardiac surgery, controlled hypotension, aortic surgery, heart failure, unstable angina, myocardial infarction and systolic hypertension in the elderly are discussed.

L14 ANSWER 21 OF 28 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 90085583 EMBASE

DOCUMENT NUMBER: 1990085583

TITLE: Southwestern Internal Medicine Conference: Clinical features, pathogenic mechanisms, and new developments in the treatment of systemic sclerosis.

AUTHOR: Geppert T.

CORPORATE SOURCE: Dept. of Internal Medicine, University of Texas, Southwestern Medical School, 5323 Harry Hines Blvd., Dallas, TX 75235, United States

SOURCE: American Journal of the Medical Sciences, (1990) 299/3 (193-209).

ISSN: 0002-9629 CODEN: AJMSA

COUNTRY: United States

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 031 Arthritis and Rheumatism

037 Drug Literature Index

LANGUAGE: English

L14 ANSWER 22 OF 28 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 89230805 EMBASE

DOCUMENT NUMBER: 1989230805

TITLE: [Isolated human venous segments as a model for the investigation of nitrate tolerance].

ISOLIERTE MENSCHLICHE VENENSEGMENTE ALS MODELL ZUR UNTERSUCHUNG VON PROBLEMEN DER NITRATTOLERANZ.

AUTHOR: Schneider W.; Hawlicek J.; Kirsten N.; Kober G.; Krause A.; Weyenmeyer T.; Satter P.; Von Loh D.; Kaltenbach M.

CORPORATE SOURCE: Abteilung für Kardiologie, Klinikum der J.W. Goethe-Universität, 6000 Frankfurt a. M. 70, Germany

SOURCE: Zeitschrift für Kardiologie, (1989) 78/SUPPL. 2 (33-37).

ISSN: 0300-5860 CODEN: ZKRDX

COUNTRY: Germany

DOCUMENT TYPE: Journal

FILE SEGMENT: 006 Internal Medicine

018 Cardiovascular Diseases and Cardiovascular Surgery

037 Drug Literature Index

LANGUAGE: German

SUMMARY LANGUAGE: English

AB Concentration-dependent relaxation (6-70%) of segments of human saphenous veins under isometric conditions could be demonstrated with cumulative concentrations of Isosorbide dinitrate (ISDN) and Glycerol trinitrate GTN (10-9-10-5 M). Vein segments were obtained during coronary bypass surgery. Nitrate (GTN)-induced relaxation was accompanied by a 2- to 3-fold increase of cyclic GMP content in the vessel walls. However, no change of concentrations in the vessel walls could be determined for the metabolites of prostaglandines: (PG E2, PG F(2.alpha.), TX B2, 6-keto-PGF(1.alpha.)). Pretreatment of patients with 40 mg ISDN (standard release formulation) 4 times daily for 1 week prior to surgery with the last dose 1 hour before harvesting the vein segments did not influence relaxation by ISDN. Immersion of vein segments for 1 hour in buffer solution containing 10-6 M ISDN (= therapeutic concentration) prior to relaxation with cumulative concentrations of ISDN did not influence relaxation either. Induction of in vitro tolerance required ISDN concentrations which exceeded the range achieved under therapeutic conditions: 4.4×10^{-4} M. This in vitro tolerance could be widely reversed by 10 mM N-Acetylcysteine (NAC) suggesting involvement of sulfhydryl (SH) groups. Since tolerance in this experimental model was not seen under concentrations achieved in patients it seems likely that clinical tolerance is caused by activation of counterregulatory forces.

L14 ANSWER 23 OF 28 MEDLINE
 ACCESSION NUMBER: 89363472 MEDLINE
 DOCUMENT NUMBER: 89363472 PubMed ID: 2475712
 TITLE: Determinants of in vitro **nitroglycerin** tolerance induction and reversal: influence of dose regimen, nitrate-free period, and sulfhydryl supplementation.
 AUTHOR: Henry P J; Horowitz J D; Louis W J
 CORPORATE SOURCE: Department of Clinical Pharmacology, Austin Hospital, Heidelberg, Victoria, Australia.
 SOURCE: JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (1989 Jul) 14 (1) 31-7.
 Journal code: K78; 7902492. ISSN: 0160-2446.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 198910
 ENTRY DATE: Entered STN: 19900309
 Last Updated on STN: 19980206
 Entered Medline: 19891004

AB The influence of dose regimen on the induction and reversal of tolerance to **nitroglycerin** (NTG) is not well understood despite the current widespread clinical use of both sustained and intermittent modes of NTG administration. In an isolated coronary artery preparation both the NTG preexposure concentration and the duration of the NTG preexposure period were positive and independent determinants of the extent of NTG tolerance induction. During a "nitrate-free" or washout period, NTG tolerance was at least partially reversible. The apparent rate of NTG tolerance reversal during a "nitrate-free" period was not dependent on the absolute degree of NTG tolerance induced or on the dose regimen used to induce NTG tolerance. In this isolated vascular

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preparation, sulfhydryl (SH) supplementation with 1 mM N-**acetylcysteine** produced no significant augmentation of NTG-induced relaxations in either NTG tolerant or non tolerant tissues. N-**acetylcysteine** was ineffectual in attenuating the development of NTG tolerance in coronary artery preparations incubated in either Krebs bicarbonate buffer or in 10% human plasma. We conclude that in this model the NTG preexposure concentration, the duration of the NTG preexposure period, and the duration of the "nitrate-free" period are critical and independent determinants of the extent of NTG tolerance but that NTG tolerance is not significantly attenuated by SH supplementation.

L14 ANSWER 24 OF 28 MEDLINE
ACCESSION NUMBER: 89013095 MEDLINE
DOCUMENT NUMBER: 89013095 PubMed ID: 2459545
TITLE: Discrepancy between initial and steady-state resistance vessel responsiveness to short-term **nitroglycerin** exposure in the hindlimb of conscious dogs.
AUTHOR: Stewart D J; Munzel T; Holtz J; Bassenge E
CORPORATE SOURCE: Department of Medicine, McGill University, Montreal, Canada.
SOURCE: JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (1988 Aug) 12 (2) 144-51.
Journal code: K78; 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198811
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19960129
Entered Medline: 19881107

AB Since much of the antianginal efficacy of **nitroglycerin** can be ascribed to its ability to dilate large arteries and venous capacitance vessels at dosages that have little steady-state effect on vascular resistance, we re-examined the reasons for low responsiveness of resistance vessels to **nitroglycerin** in a peripheral vascular bed in vivo. In chronically instrumented conscious dogs, intra-iliac **nitroglycerin** (0.15, 0.5, and 1.5 micrograms/kg/min) resulted in substantial dose-dependent initial increases in iliac flow (35% +/- 7%, 60% +/- 11%, and 106% +/- 12%, respectively). However, unlike the responses of iliac large artery diameter, these dilations were not sustained during a 6-min infusion. In contrast, doses of nitroprusside, acetylcholine, and adenosine, which gave initial dilations comparable to **nitroglycerin**, resulted in considerably greater steady-state responses (p less than 0.001). Nitrate tolerance, autoregulatory escape, reflex vasoconstriction, and the influence of cyclooxygenase products were ruled out as potential explanations of this selective pattern of **nitroglycerin** response. It is proposed that the rapid attenuation of **nitroglycerin**-induced dilation in a representative peripheral vascular bed cannot be attributed to currently accepted hypotheses and contributes more to the unique and beneficial spectrum of nitrate vascular action than an a priori lack of sensitivity of resistance vessels.

L14 ANSWER 25 OF 28 BIOSIS COPYRIGHT 2001 BIOSIS
 ACCESSION NUMBER: 1989:139551 BIOSIS
 DOCUMENT NUMBER: BA87:74204
 TITLE: PHARMACOLOGICAL STUDY ON MECHANISM OF ARTERIAL SMOOTH
 MUSCLE RELAXATION BY ORGANIC NITRATES
 NITROSO-COMPOUND AND NITROPRUSSIDE.
 AUTHOR(S): SUZUKI M
 CORPORATE SOURCE: DEP. PHARMACOL., KANSAI MED. UNIV., MORIGUCHI, OSAKA
 570.
 SOURCE: J KANSAI MED UNIV, (1988) 40 (1), 58-88.
 CODEN: KIDZAK. ISSN: 0022-8400.
 FILE SEGMENT: BA; OLD
 LANGUAGE: Japanese

AB The purpose of the present study was to determine the involvement of Ca^{2+} (Mg^{2+})-ATPase, guanylate cyclase, PGI₂ synthesis and/or glutathion in mechanism of vascular smooth muscle relaxation by nitro- and nitroso-vasodilator drugs. Vasodilators used in the experiment were **nitroglycerin** (GTN), isosorbide dinitrate (ISD), N-nitroso-N-morpholino aminoacetonitrile (SIN-1A, an active metabolite of molsidomine) and sodium nitroprusside (SNP). Guinea-pig thoracic aorta strips were suspended in tissue bath which permit continuous recording of isometric tension. Relaxation was measured in submaximally contracted strips with noradrenaline (NA, 30 μM) or PGF₂. α . (5 μM) and dose-relaxation curves were constructed to show the effects or IC₅₀ values of vasodilators. The cumulative concentrations of GTN from 0.001 to 100.0 μM and ISD from 0.01 to 100.0 μM relaxed the contracted strips in a concentration dependent manner. IC₅₀ values in GTN and ISD were 0.26 μM and 4.8 μM , respectively in the NA-contracted preparation. When tranylcypromine (TC), indomethacin (IDM) and/or 15 HPETE, each 10 μM which inhibit the production of PGI₂, were added to the bath 20 min before NA application, the relaxation by GTN or ISD was attenuated to cause a significant shift of dose-relaxation curves to the right and IC₅₀ values obtained from the curves was larger than the control one in each case. On the other hand, TC, IDM and 15 HPETE failed to alter the enhancement by GTN and ISD in Ca^{2+} (Mg^{2+})-ATPase activity in the microsome fraction from guinea-pig thoracic aorta smooth muscle. The tension developed by NA or PGF₂. α . was decreased by the cumulative concentrations of SIN-1A from 0.001 to 100.0 μM or SNP 0.001 to 100.0 μM in a concentration dependent manner. The relaxation was attenuated in the presence of methylene blue (MB) or 6-anilino-5-,8-quinolinedione (AQD), which is reported as a guanylate cyclase inhibitor. SIN-1A was found to stimulate the activity of Ca^{2+} (Mg^{2+})-ATPase in the microsome fraction from guinea-pig aorta. Inorganic nitroso complex salt. SNP in the low concentration exerted a similar effect on Ca^{2+} (Mg^{2+})-ATPase activity to SIN-1A, but not in the high concentration of the drug. MB inhibited the stimulatory effect of SIN-1A in the Ca^{2+} (Mg^{2+})-ATPase activity, while AQD had no effect on the ATPase activity. The addition of SNP to the strips in the high concentration caused a depression of contractions obtained with NA even after removal of SNP from the bath. This depression was completely reversible upon the addition of **glutathione** 100 μM or MB 1.0 μM . The effects of SNP on vascular tissue may be, in part, account for the decrease in **glutathione** content in the smooth muscle of the tissue. These results suggest that GTN and ISD elicit vasodilation, partially thorough the stimulation of Ca^{2+} pump ATPase activity and also through the accelerated

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production of PGI₂ in arterial blood vessel, and that SIN-1A and SNP dilate the blood vessel by the stimulatory effect on the Ca²⁺ pump ATPase as well as guanylate cyclase activity, although the **glutathione** content in the vascular tissue may decrease after the application of SNP because of a possible interaction between Fe³⁺-prussiate and SH-group of this active peptide.

L14 ANSWER 26 OF 28 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 88141748 MEDLINE
DOCUMENT NUMBER: 88141748 PubMed ID: 2963927
TITLE: Comparative vasorelaxing profiles of nicorandil, isosorbide dinitrate and **nitroglycerin** in isolated coronary arteries of the dog.
AUTHOR: Ohba Y; Shiraki Y; Sakai K
CORPORATE SOURCE: Department of Pharmacology, Chugai Pharmaceutical Co., Ltd., Shizuoka, Japan.
SOURCE: JAPANESE JOURNAL OF PHARMACOLOGY, (1987 Nov) 45 (3) 397-404.
Journal code: KO7; 2983305R. ISSN: 0021-5198.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198803
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19990129
Entered Medline: 19880329

AB The vasorelaxing effects of nicorandil (NCR), isosorbide dinitrate (ISDN) and **nitroglycerin** (NTG) were studied in isolated canine coronary arteries. In rings of coronary arteries precontracted with **prostaglandin** F₂ alpha (3 x 10⁻⁶ M) or KCl (30 mM), removal of the endothelium significantly augmented the relaxing effects of NCR, while it did not affect those of ISDN and NTG. In unrubbed rings precontracted with KCl (30 mM), methylene blue (5 x 10⁻⁶ M) significantly inhibited vasorelaxing responses to the three drugs. The order of the inhibition was as follows: NTG greater than ISDN greater than NCR. When the unrubbed tissue was incubated with NTG (10⁻⁵ M) or ISDN (10⁻⁴ M) for 10 min, it developed acute tolerance in relaxing response to NTG or ISDN. Unlike NTG and ISDN, NCR did not develop any tolerance. The treatment with N-acetylcysteine (5 x 10⁻⁵ M) tended to potentiate relaxant effects of NTG and to reduce the degree of acute tolerance to NTG. The results suggest that cGMP plays a role in the relaxation of the coronary artery induced by the drugs and furthermore that the mode of the vasorelaxing action of NCR may be somewhat different from that of NTG or ISDN.

L14 ANSWER 27 OF 28 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 85140979 EMBASE
DOCUMENT NUMBER: 1985140979
TITLE: The pharmacological and physiological role of cyclic GMP in vascular smooth muscle relaxation.
AUTHOR: Ignarro L.J.; Kadowitz P.J.
CORPORATE SOURCE: Department of Pharmacology, Tulane University School of Medicine, New Orleans, LA 70112, United States
SOURCE: Annual Review of Pharmacology and Toxicology, (1985) VOL. 25/- (171-191).

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COUNTRY: CODEN: ARPTDI
United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
029 Clinical Biochemistry
018 Cardiovascular Diseases and Cardiovascular
Surgery
030 Pharmacology
LANGUAGE: English

L14 ANSWER 28 OF 28 MEDLINE
ACCESSION NUMBER: 86073989 MEDLINE
DOCUMENT NUMBER: 86073989 PubMed ID: 3000161
TITLE: Hemodynamic attenuation and the nitrate-free
interval: alternative dosing strategies for
transdermal **nitroglycerin**.
AUTHOR: Flaherty J T
SOURCE: AMERICAN JOURNAL OF CARDIOLOGY, (1985 Dec 27) 56 (17)
32I-37I.
Journal code: 3DQ; 0207277. ISSN: 0002-9149.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198601
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860123

AB Various dosing strategies to determine therapeutic effects of **nitroglycerin** (NTG) preparations are reviewed. The importance of individual patient titration in establishing an effective **NTG** dosage is emphasized by reviewing a **nitroglycerin** ointment study and a crossover study. Studies reporting the development of hemodynamic attenuation ("tolerance") with longterm nitrate therapy are also discussed. The results of these and other studies suggest that the magnitude of the hemodynamic response to **NTG** or isosorbide dinitrate diminishes over time, with acute or first-dose effects far exceeding those obtained during long-term therapy. However, patients on long-term therapy continue to respond to sublingual **NTG**, which suggests that this phenomenon is not true **NTG** tolerance. The effect of a nitrate-free interval as a mechanism for avoiding hemodynamic attenuation of **NTG** therapy is reviewed. The results of 4 studies discussed found that intermittent nitrate protocols were not associated with the attenuated hemodynamic effect observed during chronic therapy. Two possible mechanisms for the vasodilatory effects of **nitroglycerin** are discussed. The first relates to the production of cyclic guanosine monophosphate in the smooth muscle cells of arteries and veins; the second to the synthesis of **prostaglandin** I₂ by vascular endothelial cells. A mechanism by which nitrate receptors could be manipulated to increase vascular responsiveness is theorized, as well as a means by which a nitrate-free interval might avoid the development of hemodynamic attenuation in terms of cellular mechanisms and receptors.

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